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(54) Title: METHOD FOR THE SCREENING OF $\alpha_2\delta$-1 SUBUNIT BINDING LIGANDS

(57) Abstract: A method for the screening of ligands which bind to soluble $\alpha_2\delta$-1 subtype polypeptides. The invention also relates to compositions and kits for implementing such methods, as well as to the ligands selected or identified using the same.

Method for the screening of $\alpha_2\delta$-1 subunit binding ligands

FIELD OF THE INVENTION

The invention relates to a method for the screening of ligands which bind a soluble secreted cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$ subunit polypeptide, in particular calcium channel $\alpha_2\delta$-1 subunit.

BACKGROUND OF THE INVENTION

Gabapentin (1-aminoethyl-cyclohexane acetic acid) is currently commercialized for the treatment of epilepsy. The compound has however been recognized as being also useful for the treatment of pain and anxiety.

Recent reports have suggested an interaction between gabapentin and the $\alpha_2\delta$ subunit of a voltage-dependent calcium channel (VDCC). But electro-physiological studies have yielded conflicting data on the action of gabapentin at VDCCs, even though the relevance of the interaction of gabapentin at the $\alpha_2\delta$ subunit to the clinical utility of the drug is becoming clearer. However, none of the prototype anticonvulsant drugs displace [^{3}H]gabapentin binding from the $\alpha_2\delta$-1 subunit.

The most frequently used assay currently available for the screening of ligands that bind the $\alpha_2\delta$ subunit involves the use of pig membrane extracts as a source of the $\alpha_2\delta$ subunit. Such an assay presents major inconvenients. Firstly, because the assay material is a membrane extract, it is very difficult to accurately determine the protein composition from one assay preparation to another particularly with regard to the subtype. Also, the presence of various impurities in the assay preparation is a problem in small plate assays. Furthermore, as the protein preparation lacks homogeneity, the interaction between the targeted protein and the assay plate is often quite uneven. This renders the streamlining of the assay in a high throughput format almost impossible to achieve.

SUMMARY OF THE INVENTION

The inventors have found that it was possible to use a soluble secreted form of a voltage-dependant calcium channel $\alpha_2\delta$-1 subunit polypeptide (hereinafter $\alpha_2\delta$-1 subunit polypeptide) in an assay for the screening of ligands which bind the $\alpha_2\delta$-1 subunit.

The exact position and configuration of the [^{3}H]gabapentin binding site on the $\alpha_2\delta$ subunit is not currently known. Furthermore, recent deletion experiments on the porcine $\alpha_2\delta$-1 subunit coding sequence have shown that amino-acids close to the C-terminal region are needed in order for the protein to bind [^{3}H]gabapentin. For this very reason, the use of truncated forms of the porcine $\alpha_2\delta$-1 subunit in screening assays has not been disclosed or suggested in the prior art because there was concern as to whether relevant levels of binding capacity would be achieved in an assay environment.

The assay of the invention is of considerable interest because it confirms that a recombinant soluble secreted $\alpha_2\delta$-1 subunit polypeptide can be used in high throughput $\alpha_2\delta$-1 ligand screening. It also provides a useful advantage over the pig membrane extract screening assay as it allows the study of $\alpha_2\delta$-1 subtype-specific binding ligands. Proteins can be tagged which makes purifying convenient and possible to use a tagged antibody for recognition.

It was not clear whether the addition of the 6His tag to the C-terminus of the protein would affect the [^{3}H]gabapentin binding properties of $\alpha_2\delta$.

It was also unclear whether a C-terminally located 6His tag on $\alpha_2\delta$ would be accessible for interaction with the Ni NTA chromatography matrix (for purification purposes) and SPA bead, or Ni flashplate well surface (for purposes of the assay).

The invention concerns a method for the screening of ligands which bind a calcium channel $\alpha_2\delta$-1 subunit.

The method comprises the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide with:
  - a ligand of interest; and
  - a labelled compound which binds a $\alpha_2\delta$-1 subunit; and

- measuring the level of binding of the labelled compound to the secreted soluble $\alpha_2\delta$-1 subunit.

The invention also concerns a method for the screening of biologically active products, in particular products that modulate a nervous system function in a subject, comprising the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide with:
  - a candidate product; and
  - a labelled compound which binds a $\alpha_2\delta$-1 subunit; and
- measuring the level of binding of the labelled compound to the secreted soluble $\alpha_2\delta$-1 subunit.

The invention also concerns a kit for the screening of ligands which bind a calcium channel $\alpha_2\delta$-1 subunit.

The kit comprises:

- a secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide; and
- a labelled compound which binds a calcium channel $\alpha_2\delta$-1 subunit.

The invention also concerns a kit or a method for the screening of ligands which bind a calcium channel $\alpha_2\delta$ subunit, a method for the screening of biologically active products, in particular products that modulate a nervous system function in a subject, characterized in that said kits or methods comprise at least one of the following compounds :

1) A calcium channel $\alpha_2\delta$ subunit that is soluble and retain the functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit from which it derives.
2) A calcium channel $\alpha_2\delta$ subunit according to 1) wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is of mammalian origin.

3) A calcium channel $\alpha_2\delta$ subunit according to 2) wherein the mammalian origin is a human, a porcine, a rat or a mouse origin.

4) A calcium channel $\alpha_2\delta$ subunit according to 3) wherein the mammalian origin is a human origin.

5) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 4) above, wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally expressed in the cerebral cortical.

6) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 5) above, wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is voltage-dependent.

7) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 6) above, wherein the $\alpha_2\delta$ subunit is cleaved.

8) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 7) above, wherein the $\alpha_2\delta$ subunit is cleaved into separate α_2 and δ peptides.

9) A calcium channel $\alpha_2\delta$ subunit according to 8), wherein the α_2 and δ peptides are disulfide-bridged.

10) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 6) above, wherein the $\alpha_2\delta$ subunit is not cleaved.

11) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 10) above characterized in that it is purified or isolated.

12) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 11) above characterized in that it is processed as the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally processed.

13) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 12) above characterized in that it is producable by the baculovirus/insect cells expression system.

14) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 13) above characterized in that it is produced by the baculovirus/insect cells expression system.

15) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 14) above characterized in that its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates

16) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 15) above characterized in that its δ peptide has a C-terminal truncation with respect to the complete δ peptide from which it originates, said truncation being sufficient to render the truncated δ peptide soluble.

17) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 16) above characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates.

18) A calcium channel $\alpha_2\delta$ subunit according to any one of 15) or 17) above characterized in that ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

19) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 18) above characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates, its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates and its δ peptide does not comprise a part of the transmembrane domain of the complete δ peptide from which it originates which renders said calcium channel insoluble.

20) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 19) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates is *$\alpha_2\delta$-1, $\alpha_2\delta$-2, $\alpha_2\delta$-3 or $\alpha_2\delta$-4.*

21) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°20.

22) A calcium channel $\alpha_2\delta$ subunit according to 20) or 21) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 4, SEQ ID N° 5 or SEQ ID N° 6.

23) A calcium channel $\alpha_2\delta$ subunit according to any one of 20) to 22) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 340 and amino acid number 1062 of SEQ ID N°20.

24) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°21.

25) A calcium channel $\alpha_2\delta$ subunit according to 20) or 24) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 10, SEQ ID N° 11 or SEQ ID N° 12.

26) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 24) or 25) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 306 and amino acid number 1019 of SEQ ID N°20.

27) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°55.

28) A calcium channel $\alpha_2\delta$ subunit according to 20) or 27) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 53, SEQ ID N° 54 or SEQ ID N° 55.

29) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 27) or 28) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1050 of SEQ ID N°55.

30) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°33 or SEQ ID N°44.

31) A calcium channel $\alpha_2\delta$ subunit according to 20) or 30) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 34, SEQ ID N° 35, SEQ ID N° 36, SEQ ID N° 41, SEQ ID N° 42 or SEQ ID N° 43.

32) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 30) or 31) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

33) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 30) or 31) above characterized in that the amino acid sequence of its unprocessed form comprises the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

34) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 30), 31), 32) or 33) above characterized in that its α_2 peptide comprises the region comprised between amino acid number 302 and amino acid number 946 or 997 of SEQ ID N°33 or of SEQ ID N°44 and its δ peptide comprises the region comprised between amino acid number 984 and amino acid number 1018 of SEQ ID N°33 or of SEQ ID N°44.

35) A calcium channel $\alpha_2\delta$ subunit characterized in that its α_2 peptide and its δ peptide have 99%, 98%, 97%, 96%, or 95% homology or identity with the α_2 peptide and the δ peptide respectively of a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 34) above.

36) A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35).

37) A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes the α_2 peptide or the δ peptide of a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35).

38) A nucleic acid molecule which hybridizes under stringent conditions with a nucleic acid molecule according to 36) or 37) above or 39) herebelow.

39) A nucleic acid molecule according to any one of 36) to 38) above which comprises SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8, SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, SEQ ID N°15, SEQ ID N°30, SEQ ID N°31, SEQ ID N°32, SEQ ID N°38, SEQ ID N°39, SEQ ID N°40, SEQ ID N°50, SEQ ID N°51, or SEQ ID N°52.

40) A vector capable of expressing a nucleic acid molecule according to any one of 36) to 39) above.

41) An expression vector comprising a nucleic acid molecule according to any one of 36) to 39) above.

42) A vector according to 40) or 41) above which is a baculovirus vector.

43) A cell comprising a nucleic acid molecule according to any one of 36) to 39) above.

44) A cell comprising a vector according to 40), 41) or 42) above.

45) A cell according to 43) or 44) above which is a mammalian cell or an insect cell.

46) A composition comprising a calcium channel $\alpha_2\delta$ subunit according to any one of 7) to 9) above and a calcium channel $\alpha_2\delta$ subunit according to 10) above.

47) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35) above, characterized in that it is tagged or labelled.

48) A nucleic acid molecule according to any one of 36) to 39) above, characterized in that it is tagged or labelled.

49) A calcium channel $\alpha_2\delta$ subunit according to 47), characterized in that it is tagged at the C-terminal part of the δ peptide.

50) A nucleic acid molecule according to 48) above, characterized in that it is tagged at the end of the region of the nucleic acid molecule encoding the C-terminal part of the δ peptide.

51) A calcium channel $\alpha_2\delta$ subunit according to 47) or 49), characterized in that it is tagged by a 6 histidine residue tagg.

52) A nucleic acid molecule according to 48) or 50), characterized in that it is tagged by a 6 histidine residue tagg.

The invention also concerns a screening assay using a compound according to any one of 1) to 52) above. This screening assay is preferably an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.

The invention also concerns the use of screening assay using a compound according to any one of 1) to 52) above to detect or measure the binding or interaction of a ligand of a

calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit. Specific ligands of interest are gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

The above screening assays or uses are preferably an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.

The invention also concerns a kit to detect or measure the binding or interaction of a ligand of a calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit characterized in that it comprises a compound according to any one of 1) to 52). Specific ligands of interest are gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

The kits of the invention recited above are usable in an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.

There is a great advantage to use imidazole in the context of the assays and kits of the invention because it increases the possibilities of interactions between the ligand and the receptor. A preferred range of use of imidazole in an SPA assay of the invention is between about 1 mM and about 50 mM. A preferred range of use of imidazole in a Flasplate assay of the invention is between about 1 mM and about 20 mM.

There is a great advantage to use Bovine Serum Albumine (BSA) in the context of the assays and kits of the invention because it renders the compounds used in these assays and kits a lot more stable and therefore allows their in large-scale screening, especially in an high-throughput screening format. A preferred range of use of BSA is between about 0.025% and about 0.05%.

A great advantage of the compounds described above which are used or comprised in the assays and kits of the invention is that they can be obtained and therefore used as an homogeneous material.

Another great advantage of the compounds described above and used or comprised in the assays and kits of the invention is that they can be obtained in large quantity by the technique of the DNA recombinant. A most preferred system to produce these compounds is the baculovirus/insect cells system which furthermore allows to obtain high yields of production.

Precise embodiments of the above kits and assays are recited in the continuation of the text of this application, especially in the examples.

The invention also resides in a product or ligand isolated, identified or selected using the above screening methods or kits, for use as a medicament or as a lead for further drug development purposes. As indicated above, the compounds are potentially useful for treating disorders of the nervous system, including epilepsy, pain and anxiety

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 represents the elution profile of the recombinant polypeptide with the amino acid sequence of SEQ ID No 37 purified by Superdex-200 chromatography, either before or after electron on NI-NTA.

Figure 2 illustrates the optimization of imidazole concentrations in an embodiment of the SPA assay of the invention. SPA assay of [^{3}H]gabapentin (18.4nM) binding to the recombinant polypeptide of amino acid sequence SEQ ID No 9 (s-$\alpha_2\delta$-1b-6His) (20µl).

Figure 3 illustrates the optimization of imidazole concentrations in an embodiment of the flashplate assay of the invention. Flashplate assay of [^{3}H]gabapentin (14nM) binding to the recombinant polypeptide of amino acid sequence SEQ ID No 37 (s-$\alpha_2\delta$-1b-6His) (10µl).

Figure 4 illustrates the flashplate time course of [^{3}H]gabapentin (13 nM) binding to various concentrations of the recombinant polypeptide with the amino acid sequence of SEQ ID No 37.

Figure 5 illustrates the capacity of the recombinant polypeptide with the amino acid sequence of SEQ ID No 37 in a flashplate assay after 3 hours of incubation.

Figure 6 illustrates the optimum imidazole concentration, assayed after 3 hours of incubation, required to maximize [^{3}H]gabapentin binding using a constant amount of the recombinant polypeptide with the amino acid sequence of SEQ ID No 37.

Figure 7 illustrates flashplate assay of [^{3}H]gabapentin saturation binding to the purified recombinant polypeptide with the amino acid sequence of SEQ ID No 37, assayed after 3 hours of incubation.

Figure 8 illustrates the flashplate time course optimisation of imidazole concentration required to maximize the [^{3}H]Leucine (10.1 nM) binding window to the purified recombinant polypeptide with the amino acid sequence of SEQ ID No 37, assayed after 3 hours of incubation.

Figure 9 illustrates competition curves of three compounds in the flashplate assay format, assayed after 3 hours of incubation (see also Table 2).

Figure 10 illustrates the dose response nature of [^{3}H]gabapentin binding to s-$\alpha_2\delta$-1b-6His in the Wheat Germ lectin flashplate assay. The level of non-specific binding is low (around 50-70cpm) and stable, independent of the volume of protein assayed or the point analysed on the time-course. The window is relatively stable over an extended period of time with just a gradual decline from the 15-hour time point (approximately 10% of the window every 24 hours).

Figure 11 illustrates the dose response nature of [^{3}H]gabapentin binding to $\alpha_2\delta$-1 and the maintenance of a constant low-level of non-specific binding (around 30-60cpm) independent of protein volume assayed.

Figure 12 illustrates the dose response nature of [^{3}H]gabapentin binding to $\alpha_2\delta$-1 in the Nickel flashplate assay. The level of non-specific binding is low (around 70-100cpm) and stable, independent of the volume of protein assayed or the point analysed on the time-course. A stable window is maintained for a period of at least 50 hours (between ~20 and 70 hours on the time-course).

Figure 13 illistrates the stability of $\alpha 2\delta$-1/[3H] gabapentin binding assay. Each well was performed in triplicate and contains in 200µl of : 0.1M HEPES pH7.3, 0.5mM Imidazole Various concentrations of BSA fraction V (0, 0.025, 0.05, 0.25, 0.5 and 1%).

Figure 14 is and example of amino acid sequence alignments of the $\alpha_2\delta$-1 deletion region in four species variants of $\alpha_2\delta$-1 splice isoform b.

DETAILED DESCRIPTION OF THE INVENTION

The invention concerns a method for the screening of ligands which bind a soluble secreted $\alpha_2\delta$ subunit polypeptide, in particular a soluble secreted $\alpha_2\delta$-1 subunit polypeptide. The term $\alpha_2\delta$ subunit polypeptide, when used herein, is intended to designate a structure containing two polypeptides (α_2 and δ) attached or associated to one another, in particular by covalent disulfide bridges. More particularly, the targeted $\alpha_2\delta$ subunit binding site is preferably the [^{3}H]gabapentin binding site. The various parameters of the method of the invention are described in further detail below.

A – Secreted soluble recombinant $\alpha_2\delta$-1 subunit polypeptide

Several nucleotide sequences encoding a secreted soluble form of an $\alpha_2\delta$-1 subunit can be used in the context of the present invention. Preferred soluble secreted $\alpha_2\delta$-1 subunit polypeptides are derived from eukaryotic $\alpha_2\delta$-1 subunits, more preferably from mammal, such as mouse, rat, rabbit, porcine, bovine or others and human $\alpha_2\delta$-1 subunits. Most preferred soluble secreted $\alpha_2\delta$-1 subunit polypeptides are derived from the human or porcine $\alpha_2\delta$-1 subunits.

More specifically, the selected nucleotide sequences encode a secreted soluble polypeptide having at least 80%, preferably 90%, more preferably 95%, and most preferably 98 or 99% amino-acid identity with the polypeptide comprising from amino acid 1 to between amino-acids 985 and 1087 of SEQ ID N°33 or SEQ ID N°44, preferably between amino-acids 985 and 1085, more preferably between amino-acids 985 and 1078, most preferably between amino-acids 985 and 1064, 1059 or 1044 of SEQ ID N°33 or SEQ ID N°44.

In particular embodiments, selected nucleotide sequences encode a secreted soluble polypeptide having at least 80%, preferably 90%, more preferably 95%, and most preferably 98 or 99% amino-acid identity with the polypeptide comprising from amino acid 1 to between amino-acids 1008 and 1087 of SEQ ID N°33 or SEQ ID N°44, in particular between 1018 and 1078, specifically between 1043 and 1078.

More specifically, the selected nucleotide sequences encode a secreted soluble polypeptide having at least 80%, preferably 90%, more preferably 95%, and most preferably 98 or 99% amino-acid identity with the polypeptide comprising from amino acid 1 to between amino-acids 985 and 1054, preferably between amino-acids 985 and 1059, and most preferably between amino-acids 1019 and 1044 of SEQ ID N°33 or SEQ ID N°44.

In order to determine the optimal deletions on the $\alpha_2\delta$-1 subunit cDNA that yield a soluble secreted polypeptide devoid of membrane anchorage structures and having a functional [^{3}H]gabapentin binding site, the inventors tested the expression of several human or porcine $\alpha_2\delta$-1 subunit cDNA deletion mutants. The discussion provided below provides detailed comments on possible truncations, giving as an example the porcine $\alpha_2\delta$-1 subunit. However, given the very substantial cross-species homology for $\alpha_2\delta$-1 subunit sequences, the comments below can also be applied to other eukaryotic species, and more particularly other mammalian species such as the rat, the mouse or the rabbit. Their $\alpha_2\delta$-1 subunit sequences, which are available in public databases, share a very substantial homology with the human and porcine $\alpha_2\delta$-1 subunit sequences. Therefore, the inventore believe that this succesefull identification and characterization of a region in $\alpha_2\delta$-1 which can be modified to produce a soluble $\alpha_2\delta$-1 of pig and human whilst maintaining Gabapentin binding, enables those skilled in the art to modify other species $\alpha_2\delta$-1 polypeptides. Exambles of this modification site in other $\alpha_2\delta$-1 from other species is shown in figure 14.

The inventors found that by deleting from the porcine $\alpha_2\delta$-1 subunit cDNA a nucleotide sequence encoding as much as amino-acids 967 to 1091 of the native protein, soluble polypeptides could be obtained. On the other hand, the minimal deletion required to achieve solubility appears to be located around nucleotides encoding amino-acids 1064

to 1091 of the sequence of SEQ ID N°33. In this regard, the mutant polypeptide expressed using a cDNA deletion mutant from which a sequence encoding amino-acids 1064 to 1091 is removed is found in both soluble and membrane-associated forms, with [^{3}H]gabapentin and/or other derivatives or compounds such as pregabalin and gabapentoids binding properties similar to that of the wild type protein. Furthermore, a mutant protein expressed using a cDNA deletion mutant from which a nucleotide sequence encoding amino-acids 1085 to 1091 is removed recovers its membrane anchorage properties. Also, mutant proteins expressed using cDNA deletion mutants from which nucleotide sequences encoding either amino-acids 1037 to 1091 or amino-acids 1019 to 1091 of SEQ ID N°33 or 44 are removed are found in soluble form.

The inventors believe that the soluble secreted $\alpha_2\delta$-1 subunit polypeptides which are as close as possible to the native sequence and which are therefore more likely to retain their native folding and hence their [^{3}H]gabapentin- binding properties are those corresponding to a protein in which amino-acid stretch 985-1091 to 1074-1091, the amino-acid sequence of SEQ ID N°33 or 44 has been deleted. The skilled scientist can quite easily determine within this amino-acid stretch the optimal mutant protein.

The invention therefore particularly concerns a screening assay in which the secreted soluble $\alpha_2\delta$-1 subunit polypeptide is preferably a polypeptide having at least 80% identity with the polypeptide comprising from amino-acid 1 to between amino-acid 985 and 1054, preferably between amino-acids 985 and 1059, and most preferably between amino-acids 1019 and 1064 of SEQ ID N°33 or SEQ ID N°44. Preferred $\alpha_2\delta$-1 subunit polypeptides which can be used in the present invention are those of SEQ ID N°34, 35, 36, 37, 41, 42 and 43, with the polypeptides of SEQ ID N°33 and SEQ ID N°43 being most preferred.

In a first and preferred embodiment of the invention, the $\alpha_2\delta$-1 subunit polypeptide is purified before it is used in the assay. The purification step, an example of which is provided further in this specification, can be carried out using several purification techniques well-known to the skilled person.

In some instances, it is required to tag the $\alpha_2\delta$-1 subunit polypeptide prior to purification. The tag is then in most instances encoded into the nucleotide sequence that is needed to

express the polypeptide. Examples of such tags include, but are not limited to sequences encoding C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST. Most of these tags can be incorporated directly into the sequence, for instance through PCR amplification by incorporating the appropriate coding sequence in one of the PCR amplification primers. However, the tag can also be introduced by other means such as covalent binding of the appropriate nucleic acid sequence encoding the tag moiety with the 5' or 3' end of the nucleic acid sequence encoding the polypeptide sequence. This is the case for GST. It should be noted that the tag can be located at either end of the polypeptide sequence. Furthermore, in some instances, it can be advantageous to insert a cleavage site between the tag and the polypeptide sequence in order to permit removal of the tag sequence if needed. Therefore a first object of this invention of the invention is the use of C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST taggs for the purification and screening of $\alpha_2\delta$-1. Preferably, the use of C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST taggs for the purification and screening of $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 or 38. More preferably, the use of a sequence of histidine residues tagg for the purification and screening of $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 or 38, more preferably, the use of a sequence of 6 histidine residues tagg for the purification and screening of $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 or 38 and most preferably the use of C-terminal a 6 histidine residues tagg of $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 or 38 for the purification and screening

A secont object of the invention is the use of nucleic acids encoding C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST taggs for the purification and screening of expressed $\alpha_2\delta$-1. Preferably, the use of nucleic acids encoding C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST taggs for the purification and screening of expressed $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 or 38. More preferably, the use of nucleic acids encoding a sequence of histidine residues tagg for the purification and screening of an expressed $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 or 38, more preferably, the use nucleic acid sewuence encoding a sequence of 6 histidine residue tagg for the purification and screening of an expressed $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 or 38 and most preferably the use of C-terminal a nucleic acid sequence encoding 6 histidine residue tagg of

expressed $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 or 38 for purification and screening

In other cases, providing a tag to the polypeptide is not needed. For instance, the protein can be purified using affinity columns loaded with specific monoclonal antibodies.

In a second embodiment of the invention, the $\alpha_2\delta$-1 subunit polypeptide can be only partially purified. For instance, it can be purified along with other contaminating proteins using an appropriate chromatography matrix such as ion-exchange chromatography column. In such instances, it is not required to tag the desired polypeptide of interest.

The most preferred embodiment contemplated by the inventors concerns the use of a purified tagged $\alpha_2\delta$-1 subunit polypeptide. A particularly preferred tag is a nucleotide sequence encoding from 2 to 10, and preferably 6 histidine residues as provided in the polypeptide of SEQ ID No 37.

The polypeptide may be prepared by expression of the corresponding nucleic acid molecule in any appropriate host cell, using various vector systems known to the skilled person. Typical examples of suitable cells include prokaryotic and eucaryotic cells, such as bacteria, yeasts, mammalian cells (including human cells), insect cells, etc. The vector may be a plasmid, virus, episome, phage, etc. As illustrated in the examples, the polypeptide can be produced for instance by expression of the nucleic acid in insect cells, using a baculovirus vector.

A most preferred system of expression of the calcium channel $\alpha_2\delta$ of the invention is the baculovirus/insect cell system. In fact, this system of expression allows to produce only the soluble form, is easy to use because the insect cells can be cultured without adherency and results in very high yield of production. Thus, this system allows mass-production of the calcium channel $\alpha_2\delta$ of the invention, provides an homogeneous production and is therefore particularly suitable for the preparation of this target for screening, in particular for high-throughput screening.

With regard to the $\alpha_2\delta$-1 subunit polypeptide used subsequently in the screening assay of the invention, several possibilities are also open to the skilled person.

In a first and preferred embodiment, the $\alpha_2\delta$-1 subunit polypeptide comprises a tag moiety which can be selected among the tags referred to above. Such tagged polypeptides are particularly useful in SPA or flashplate assays. A preferred tag is the nucleotide sequence encoding histidine residues referred to above.

In a second embodiment, the $\alpha_2\delta$-1 subunit polypeptide can be used without a tag. This is the case for instance in SPA or flashplate assays comprising beads or plates coated with wheat germ lectin. In such an embodiment, the tag is not needed as the carbohydrate moieties of the $\alpha_2\delta$-1 subunit polypeptide bind directly to the wheat germ lectin-coated beads or plates.

B - Labelled compounds which bind the $\alpha_2\delta$-1 subunit polypeptide

In cases where the $\alpha_2\delta$-1 binding site is the [^{3}H]gabapentin binding site, the preferred labelled compound which can be used is of course gabapentin itself. However, gabapentin is not the only labelled compound which can be used in this context. Indeed, it has been previously demonstrated that saturation binding analyses on porcine synaptic plasma cerebral cortex membranes performed in the presence of L-leucine indicate a competitive interaction of the amino acid with the [^{3}H]gabapentin binding site, significantly reducing [^{3}H]gabapentin binding affinity for the site. The inventors believe that this competitive interaction is true across all the amino-acids listed in table 1 below.

Table 1

Binding affinities of selected amino acids (IC_{50} <500nM) for the [^{3}H]gabapentin site in porcine cortical membranes

COMPOUND	IC_{50} (NM) ARITHMETIC MEAN (N=3) ± S.E.M.
Gabapentin	42.1 ± 5.5
L-Norleucine	23.6 ± 6.7
L-Allo-Isoleucine	32.8 ± 6.0

L-Methionine	49.6 ± 10.0
L-Leucine	61.3 ± 20.9
L-Isoleucine	68.8 ± 1.9
L-Valine	330 ± 18
L-Phenylalanine	351 ± 89

It is therefore possible to use commercialy available labelled forms of these high affinity ligands in replacement of gabapentin. The utility of [^{3}H]L-leucine has been demonstrated in a filter binding assay and in a flashplate assay format. The inventors believe that labelled amino acids but also other compounds, with affinities preferably below 500 nM in the binding assay can be used as replacements of gabapentin.

With regard to the label, several embodiments can be used in the context of the invention. Preferred labels are of course radioactive labels, a list of which is provided further in this specification.

An object of this invention is the use of labelled compounds which have an affinity of less than 500nm for the gabapentin binding site of α2δ-1 for the screening of ligands that bind to α2δ-1, preferably the use of labelled of Gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine or L-Phenylalanine, more preferably the use of labelled Gabapentin.

C - Assay formats and conditions

Several assay formats can be used to carry out the method of the present invention. Preferred assay formats include scintillation assays such as the scintillation proximity assay (SPA) or the flashplate assay. Other assay formats well known to those skilled in the arts such as the filter binding assay and the centrifugation assay are also contemplated in the present invention.

SPA and flashplate assays are preferred assay formats for the present invention. Additional details on these assays are provided below.

Scintillation assay format

Scintillation assays technology either involves the use of scintillant beads (for the SPA assay) or plates (for the flashplate assay). SPA beads are usually made from either cerium-doped yttrium ion silicate (y2SiO5:Ce) or polyvinyltoluene (PVT) containing an organic scintillant such as PPO. Flashplates commonly used are those such as Ni chelate flashplates although other flashplates can also be used.

Assays are usually carried out in aqueous buffers using radioisotopes such as ^{3}H, ^{125}I, ^{14}C, ^{35}S or ^{33}P that emit low-energy radiation, the energy of which is easily dissipated in an aqueous environment. For example, the electrons emitted by ^{3}H have an average energy of only 6 keV and have a very short path length (-1 ~tm) in water. If a molecule labelled with one of these isotopes is bound to the bead or flashplate surface, either directly or via interaction with another molecule previously coupled to the bead or flashplate, the emitted radiation will activate the scintillant and produce light. The amount of light produced, which is proportional to the amount of labelled molecules bound to the beads, can be measured conveniently with a liquid scintillation (LS) counter. If the labelled molecule is not attached to the bead or a flashplate surface, its radiation energy is absorbed by the surrounding aqueous solvent before it reaches the bead, and no light is produced. Thus, bound ligands give a scintillation signal, but free ligands do not, and the need for a time- consuming separation step, characteristic of conventional radioligand binding assays, is eliminated. The manipulations required in the assays are reduced to a few simple pipetting steps leading to better precision and reproducibility.

The conditions under which SPA and flashplate assays are performed in the context of the present invention are provided below.

Scintillation assay conditions

1) SPA assay

The SPA assays is first developed to optimize the conditions under which the radioligand binds the $\alpha_2\delta$-1 subunit polypeptide. The parameters which can be varied to optimize radioligand binding in a typical SPA assay using Amersham beads include assay temperature, $\alpha_2\delta$-1 subunit polypeptide interaction with the radioligand and the SPA beads, radioligand concentration as well as pH variations.

The temperature at which the assay can be carried out can vary from 1 to 30°C. Preferred temperatures range from 18 to 23°C, with 21°C being the most preferred temperature. The interaction of the $\alpha_2\delta$-1 subunit polypeptide with the SPA beads can be optimized by adjusting the concentration of the polypeptide and by introducing a reagent which will favor this interaction. When 50 mg of Amersham SPA beads are used, the $\alpha_2\delta$-1 subunit polypeptide concentration may vary from 0.1 to 10 pmoles per well, with the optimal concentration being generally around 5 to 6 pmoles per well.

As for the reagent favoring the interaction between the $\alpha_2\delta$-1 subunit polypeptide and the radioligand as well as the Amersham SPA beads, the inventors found that imidazole could be efficiently used for that purpose when the $\alpha_2\delta$-1 subunit polypeptide is tagged with an amino acid sequence including 6 histidine residues. Furthermore, and more importantly, it was found that imidazole also enhanced binding of the radioligand to the $\alpha_2\delta$-1 polypeptide.

The optimal concentration of imidazole used to enhance radioligand binding varies depending on the concentration of $\alpha_2\delta$-1 subunit polypeptide used in the assay. For instance, when the volume of the $\alpha_2\delta$-1 subunit polypeptide is about 20 µl ($\alpha_2\delta$-1 polypeptide concentration of 0.6 pmol/ul), imidazole concentrations ranging from 10 to 50 mM can be used, with concentrations ranging between 10 and 30 mM being preferred. A most preferred imidazole concentration is 20 mM. It is to be noted that other compounds such as histidine can be used to enhance radioligand binding. Furthermore, pH variations can also influence radioligand binding although pH variations should be closely monitored as they may have an effect on the structural configuration of the of $\alpha_2\delta$-1 subunit polypeptide. Although the use of imidazole is preferred to enhance radioligand binding, the person skilled in the art knows that the use of imidazole is preferred but is absolutely not essential.

The concentration of the radioligand is evaluated with respect to the concentration of $\alpha_2\delta$-1 subunit polypeptide present in the assay medium. Generally, the concentration of radioligand varies from 1 nM to 100 nM. A preferred [^{3}H]gabapentin concentration is

about 5 to 20 nM, with a most preferred concentration being about 10 nM. A preferred [^{3}H]leucine concentration is also about 5 to 20 nM, with a most preferred concentration being about 10 nM. It is to be noted that the concentration of other radioligands having affinities similar to those of [^{3}H]gabapentin and [^{3}H]leucine should also be in the range of about 5 to 20 nM.

Once the optimal radioligand binding conditions have been determined, a test ligand can be introduced in the assay medium to evaluate the level of displacement of the radioligand. The concentration of test ligand to be introduced in the assay medium usually varies from 0.1 nM to about 100 µM. A preferred test ligand concentration of about 10 µM is usually a starting point in a high throughput screening assay. Then, depending on the number of hits obtained, it may be lowered or increased.

It is to be noted that the parameters set forth above, which have been evaluated for a typical SPA assay using Amersham SPA beads can be adjusted by the skilled person, for example if SPA beads of a different type are used.

2) Flashplate assay

Similarly to the SPA assays, the flashplate can first be developed in order to optimize the conditions under which the radioligand binds the $\alpha_2\delta$-1 subunit polypeptide. The parameters which can be varied to optimize radioligand binding in a typical flashplate assay using NEN Ni chelate flashplates or Wheat Germ lectin flashplates also include assay temperature, $\alpha_2\delta$-1 subunit polypeptide interaction with both the radioligand and the flashplates, radioligand concentration as well as pH variations.

The temperature at which the assay can be carried out can vary from 1 to 30°C. Preferred temperatures range from 18 to 23°C, with 21°C being the most preferred temperature.

The interaction of the $\alpha_2\delta$-1 subunit polypeptide with the flashplates can be optimized by adjusting the concentration of the polypeptide and by introducing a reagent which will favor this interaction. When a standard NEN Ni chelate flashplate is used, the $\alpha_2\delta$-1 subunit polypeptide volume usually varies between 0.5 and 20 µl for a concentration of

$\alpha_2\delta$-1 subunit polypeptide of 0.6 pmol/µl. As the published maximum binding capacity of NEN plates is about 6 pmol per well, the inventors consider that an optimal concentration of $\alpha_2\delta$-1 subunit polypeptide is probably around 5 pmol per well at 8µl.

Although the use of imidazole is preferred to enhance radioligand binding, the person skilled in the art knows that the use of imidazole is preferred but is absolutely not essential.

With regard to the reagent favoring the interaction between the $\alpha_2\delta$-1 subunit polypeptide and the radioligand as well as the flashplates, the inventors found that imidazole could also be efficiently used for that purpose when the $\alpha_2\delta$-1 subunit polypeptide is tagged with an amino acid sequence including 6 histidine residues. It was also found that imidazole concentrations substantially enhanced binding of the radioligand to the $\alpha_2\delta$-1 polypeptide. The optimal concentration of imidazole used to enhance radioligand binding varies depending on the concentration of $\alpha_2\delta$-1 subunit polypeptide used in the assay. For instance, when the volume of the $\alpha_2\delta$-1 subunit polypeptide is about 10 µl ($\alpha_2\delta$-1 polypeptide concentration of 0.6 pmol/µl), the optimal imidazole concentration can vary between 1 and 20 mM, with a concentration of about 10 mM being preferred. As mentioned previously, other compounds such as histidine as well as pH variations may be used to enhance radioligand binding.

The concentration of the radioligand is evaluated with respect to the concentration of $\alpha_2\delta$-1 subunit polypeptide present in the assay medium. Generally, the concentration of radioligand varies from 1 nM to 100 nM. A preferred [^{3}H]gabapentin concentration is about 5 to 20 nM, with a most preferred concentration being about 10 nM. A preferred [^{3}H]leucine concentration is also about 5 to 20 nM, with a most preferred concentration being about 10 nM. It is to be noted that the concentration of other radioligands having affinities similar to those of [^{3}H]gabapentin and [^{3}H]leucine should also be in the range of about 5 to 20 nM.

Once the optimal radioligand binding conditions have been determined, a test ligand can be introduced in the assay medium to evaluate the level of displacement of the radioligand. The concentration of test ligand to be introduced in the assay medium

usually varies from 0.1 nM to about 100 μM. A preferred test ligand concentration of about 10 μM is usually a starting point in a high throughput screening assay. Then, depending on the number of hits obtained, it may be lowered or increased.

The inventors have tested the displacement of a particular radioligand, [^{3}H]gabapentin, with (S+)-3-isobutyl gaba, (R-)-3-isobutyl gaba and gabapentin. The data provided in the examples which follow clearly shows that the assay can be used in high throughput competition studies.

Example 1

Construction of a nucleotide sequence encoding the putative soluble porcine $\alpha_2\delta$-1b deletion mutant of SEQ ID N°37

a) Primer design

PCR primers were designed to generate the soluble porcine $\alpha_2\delta$-1b deletion mutant of SEQ ID N° 37 as follows:

5' PCR primer: This was designed to engineer in a KOZAK translation initiation consensus sequence prior to the coding sequence (Kozak *JBC* **266** 19867-19870)

3' PCR primer: This was designed to engineer in six histidine residues followed by a stop-codon at the desired location in the coding sequence. In addition to the stop codon the $\alpha_2\delta$-1 primers also included an *Eco* RI restriction site.

The bold region in each primer sequence denotes the 'tagged' region; addition of sequences not present in the template. Primers were custom synthesized by Perkin Elmer Applied Biosystems UK to the ABI ready pure grade, supplied lyophilized then resuspended to 15μM in 10mM TE. JB189 and 195 were provided without 5' phosphate groups:

5' primer JB189 (5'-**TCGCCA**CCATGGCTGCTGGCTGCCTGCTG-3', SEQ ID N°20)

3' primer JB195 (5'-**TCGGAATTCCTCAGTGATGGTGATGGTGATG**AGAAACACCACCACAGTCG GT-3', SEQ ID N°21)

Could you please check the bolded regions?

b) PCR protocols for the generation of the $\alpha_2\delta$–1 deletion mutant

1) Generation of the pcDNA3-porcine-$\alpha_2\delta$–(+) PCR template

An oligo dT-primed λgt10 porcine cerebral cortical cDNA library was screened by ECL (Amersham) using a 2,381-bp *HindIII fragment* (coding sequence 268-2649) of the rabbit skeletal muscle $\alpha_2\delta$ clone (pcDNA3-Rab-$\alpha_2\delta$-(+) (supplied by Neurex) as the probe.

A positive insert was identified and subcloned into pBluescript-SK-(+) to generate pB-PC-$\alpha_2\delta$-1.1. The clone was sequenced on both strands, except for a 711-bp stretch at one end of the clone, which had a high degree of homology to mitochondrial C oxidase.

The $\alpha_2\delta$ coding region was homologous to the 3' region of the human neuronal $\alpha_2\delta$ sequence but lacked 926 bp of 5' coding sequence. The missing sequence was obtained by 5'-RACE using total RNA prepared from porcine cerebral cortex. RACE was performed across a *Bgl* I site unique in known $\alpha_2\delta$ sequences (rabbit (accession no. M21948)), rat (accession number M86621), human (accession no. M76559)

The sequence derived from the 5' RACE product was used to design a primer (JB042, 5'-GGGGATTGATCTTCGATCGCG-3'; SEQ ID N°18) specific for the 5'-untranslated end of the cDNA. PCR was then performed with *Pfu* DNA polymerase using JB042 and a primer downstream of the *Bgl* I site (JB040, CTGAGATTTGGGGTTCTTTGG, SEQ ID N°19).

The PCR product was ligated to Eco RI linkers (5'-GGAATTCC-3') and then digested with Eco RI and *Bgl* I. The 1,564-bp fragment (5' portion of the $\alpha_2\delta$ cDNA) was gel-purified.

Similarly, a 2,303-bp fragment (3' portion of the $\alpha_2\delta$ cDNA) was isolated after digestion of pB-PC-$\alpha_2\delta$-1.1 with *Bgl* I and Eco RI. The two fragments of $\alpha_2\delta$ cDNA were then ligated to EcoRI-digested pcDNA3 in a three-way ligation. A clone was picked with the full-length $\alpha_2\delta$ sequence in the positive orientation with respect to the cytomegalovirus promoter (pcDNA3-PC-$\alpha_2\delta$-(+)).

2) PCR protocol

The following reagents were added to obtain two cocktails labelled 'lower' and 'upper' buffers.

Lower	*µl*
10x *Pfu* DNA polymerase buffer	25
10mM dNTP's	5
100ng/µl pcDNA3-porcine-$\alpha_2\delta$-(+)	10
15µM JB189	8.5
15µM JB195	8.5
H_2O	193

Upper	*µl*
10x *Pfu* DNA polymerase buffer	25
H_2O	220
2.5units/µl *Pfu* DNA polymerase	5

50µl aliquots of lower buffer were added to each of four 0.5ml eppendorf tubes. To each was added one PCRgem 100 ampliwax bead (PE biosystems). Tubes were heated to 80°C for 2 minutes then cooled to 4°C. 50µl of upper buffer was then added to each tube. Tubes were then cycled on a Stratagene Robo-Cycler according to the following conditions: 98°C / 1min 30sec, followed by: for 20 cycles 98°C / 45sec, 54°C / 2min, 72°C / 6min, followed by: 72°C / 20min, followed by: hold at 4°C.

The 3228bp PCR product was then purified on a QIAquick PCR purification column (Qiagen) and eluted with 61µl of H_2O. The following reagents were added to the eluted DNA: 0.7µl 10mM ATP, 7µl 10x Polynucleotide Kinase buffer, 1µl 1unit/µl Polynucleotide Kinase.

The above 5' phosphorylation reaction was incubated at 37°C for 1 hour. The reaction was stopped by incubation at 65°C for 10min. The 3228bp 5' phosphorylated PCR product was then gel purified from a 1% agarose gel using QIAEX (Qiagen) beads and eluted in ~50µl.

Example 2

Cloning of the PCR fragments of Example 1 into the Baculovirus transfer vector pFastBac1

The PCR products of Example 1 (3228bp JB189/JB195 derived PCR product coding for 6His tagged porcine $\alpha_2\delta$-1b: SEQ ID No 9) were cloned into *Stu* I digested, calf intestinal phosphatase dephosphorylated, phenol chloroform extracted and QIAEX gel purified pFastBac1 (Life Technologies) using the Rapid DNA ligation kit (Roche Diagnostics) transforming XL1-blue ($\alpha_2\delta$-1b) *E. Coli* cells:

a) Screening for positive recombinants

Given that the PCR product was cloned by blunt-end ligation a screen was required to select a recombinant with the gene ligated in the positive orientation with respect to the polyhedrin promoter in pFastBac1. This was achieved by restriction digest of miniprep DNA (Qiagen miniprep kit) prepared from colony minicultures and analysis on a 1% TAE agarose gel. A positive clone was identified according to the following digest patterns:

SEQ ID No 9 in pFastBac1
Eco RI digest performed on miniprep DNA

	Predicted fragments (bp)
PCR product cloned in a positive orientation	4773 and 3230
PCR product cloned in a negative orientation	7989 and 14

b) Sequencing analysis of selected clones

One positive was selected for this clone and used to prepare a plasmid DNA stock of the desired construct (QIAGEN maxi kit). Confirmatory sequence reactions were performed using the Big Dye terminator sequencing kit and run on an ABI 310 Prism Genetic Analyzer. Sequence analysis of both coding strands was performed using a selection of sequencing oligonucleotide primers and has yielded the following results:

Sequencing of pFBac-Porcine-s-$\alpha_2\delta$-1-Δ1064-1091-6His confirmed that the insert sequence corresponded to the nucleic acid encoding the polypeptide of SEQ ID No 37, except for the deletion of two bases from the 5' end of the 5' PCR primer (JB189). The

loss of these two bases did not have any impact on the 5' end of the gene as the KOZAK translation start-site consensus sequence (GCCACC) starts immediately after this deletion.

Example 3

Protocol for establishing baculovirus banks for the expression of the $\alpha_2\delta$–1 deletion mutant of SEQ ID N°9

Essentially, the protocol used to generate the baculovirus banks is that outlined in the Life Technologies Bac-to Bac™ baculovirus expression systems manual.

a) Transposition of DH10Bac *E Coli* cells

One ng (5µl) of the recombinant pFastBac-1 construct containing the nucleotide sequence encoding the porcine $\alpha_2\delta$-1 deletion mutant of SEQ ID No 37 was added to 100µl of DH10Bac cells thawed on ice. The cells were then mixed gently by tapping the tube then incubated on ice for 30 minutes before heat shock treatment by incubation in a 42°C water bath for 45 seconds. The mixture was then chilled on ice for 2 minutes before the addition of 900µl of S.O.C. medium. The mixture was then placed in a shaking incubator (200rpm) at 37°C for 4hours. The cells were then serially diluted (10 fold dilutions from 10^{-1} to 10^{-3}) and 10µl of each dilution plated on LB agar plates containing 50µg/ml kanamycin, 7µg/ml gentamicin, 10µg/ml tetracycline, 100µg/ml Bluo-gal and 40µg/ml IPTG. The plates were incubated at 37°C for between 1 and 3 days until discrete colonies of blue and white colour were discernible.

b) Isolation of recombinant DNA

White colonies (containing the recombinant bacmid) were picked and grown for 24 hours (to stationary phase) at 37°C with shaking (200 rpm) in 2ml of LB containing 50µg/ml kanamycin, 7µg/ml gentamicin and 10µg/ml tetracycline. 1.5ml of culture was then transferred to a microfuge tube and centrifuged at 14,000xg for 1minute. The supernatant was removed and the cells resuspended gently in 0.3ml of 15mM Tris-HCl (pH8.0), 10mM EDTA, 100µg/ml RNase A. 0.3ml of 0.2N NaOH, 1% SDS was then added and the mixture mixed gently before incubation at 22°C for 5 minutes. Then 0.3ml of 3M potassium acetate (pH5.5) was added and the sample placed on ice for 10 minutes. After

centrifugation at 14,000 x g for 10 minutes the supernatant was transferred to a tube containing 0.8ml of isopropanol, mixed then placed on ice for 10 minutes before centrifugation at 14,000 x g for 10 minutes. The supernatant was then discarded and the pellet rinsed with 0.5ml of 70% ethanol before centrifugation at 14,000 x g for 5 minutes. This 70% ethanol rinse was then repeated before removing all of the supernatant and air drying the pellet for 10 minutes at room temperature. The pellet was finally resuspended in 40µl of TE.

c) Transfection of sf9 cells with the recombinant bacmid DNA

A 6-well tissue culture plate was seeded with $0.9x10^6$ sf9 cells (cells at log phase having grown from a culture passaged at $0.3x10^6$ cells/ml) per 35mm well in 2ml of Sf-900 II SFM media containing 50units/ml penicillin and 50µg/ml streptomycin. Cells were left to attach at 27°C for 1 hour. Bacmid DNA prepared as described above (5µl) was added to 200µl of Sf-900 II SFM media containing 6µl of CELLFECTIN and mixed before incubation at room temperature for 45 minutes. The cells were washed once with 2ml of Sf-900 II SFM media without antibiotics then 0.8ml of Sf-900 II SFM media was added to each tube containing the lipid-DNA complex. The wash buffer was removed from the cells and the 1ml of diluted lipid-DNA complex overlaid on the cells. The cells were incubated for 5hours at 27°C after which time the transfection mixture was removed and 2ml of Sf-900 II SFM media containing 50units/ml penicillin and 50µg/ml streptomycin was added. The cells were then incubated for 72 hours.

After incubation for 72 hours the media was removed from the cells and centrifuged at 500xg for 5 minutes. The supernatant was then transferred to a fresh tube, this was labelled as the P0 bank and stored at 4°C in the dark. The P1 bank was prepared by passaging sf9 cells at approx $5x10^6$ cells/ml to $2x10^6$ cells/ml (100ml in a 250ml Erlenmeyer flask) and adding 0.5ml of the P0 bank harvested above. The cells were then incubated shaking (200rpm) at 27°C for 4 days. Under sterile conditions the culture was centrifuged at 500xg for 10 minutes and the supernatant 0.2µM filtered (P1 bank). The P2 bank was prepared by adding 2ml of P1 bank per 400ml culture (in 1L Erlenmeyer flasks) passaged as above to $2x10^6$cells/ml. The culture was incubated as before for 4

days and the supernatant harvested and filtered as described for the P1 bank. The supernatant was first pooled then aliquoted (10ml) and stored at 4°C.

Example 4

Protein expression

To sf9 cells passaged from ~$5x10^6$ cells/ml to $2x10^6$ cells/ml in Sf-900 II SFM media was added 0.1ml virus per 100 ml of cells of the appropriate viral bank (400ml volumes in 1L Erlenmeyer flasks). The cells were then cultured for 4-5 days at 27°C with 110 rpm shaking. Expression of the protein was confirmed by SDS-PAGE and Western blotting using an anti penta-His monoclonal antibody (Qiagen) and was detected in the culture supernatant and cell lysate.

Example 5

Purification of $\alpha_2\delta$-1deletion mutant of SEQ ID N°37

The-$\alpha_2\delta$-1deletion mutant of SEQ ID N°37 was purified from the cell lysate following the purification strategy outlined below:

The culture was centrifuged at 6,000xg for 10 minutes and the supernatant removed. The weight of the cell pellet was determined before re-suspension in 20mM Tris pH8.0, 100mMKCl, 1% P40-Nonidet (100ml per 20g of wet cells). A protease inhibitor cocktail (Sigma, Cat# P8849), 1ml/L, was added to the mixture. The solution was then stirred for 10 minutes before centrifugation for 1hour at 30,000xg and 4°C. The supernatant was concentrated (30kDa cut off) to approx. ~300ml then centrifuged for 1hour at 100,000xg.

Supernatant containing the soluble proteins was diluted 1:3 in 10mM Tris-HCl pH8.0 (equilibration buffer) and loaded onto a pre-equilibrated Q-Sepharose column (2.5cm i.d. x 30cm h.) at a flow rate of 900ml/h. After washing with equilibration buffer until a stable A_{280nm} baseline had been achieved, protein was eluted with 20mM Tris-HCl pH8.0, 0.5M KCl, 10mM Imidazole.

The eluate was then loaded onto a Ni-NTA (Qiagen) column (2.5cm i.d. x 6cm h.) pre-equilibrated in 20mM Tris pH8.0, 0.5M KCl, 10mM Imidazole at a flow rate of 2

ml/min. The column was washed successively with buffer A (20mM Tris pH8.0, 0.5M KCl, 20mM Imidazole), buffer B (100mM Tris-HCl pH8.0, 1M KCl), and buffer A again. Elution was performed with buffer C (20mM Tris-HCl pH8.0, 100mM KCl, 0.5M Imidazole). The Ni-NTA eluate (~50ml) was concentrated (30kDa cut-off) to ~2ml and applied at 1ml/min and in 0.2ml aliquots, to an FPLC Superdex-200 column equilibrated in 10mM HEPES, pH7.4, 150mM NaCl. Fractions containing the polypeptide of SEQ ID No 37 were pooled. As shown in Figure 1, the protein elution profile and associated [^{3}H]gabapentin binding activity is presented together with a silver-stained SDS-PAGE gel (post Ni NTA load of Superdex-200) demonstrating the co-elution of the ~130kDa band ($\alpha_2\delta$) with the [^{3}H]gabapentin binding activity and A_{280nm} profile.

Example 6

SPA assay of [^{3}H]gabapentin binding to soluble porcine $\alpha_2\delta$-1b-6His

The assay was carried out at 21°C. Assay components were added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C) to 96-well Optiplates)

25µl imidazole at various concentrations (diluted from a 1M stock pH8.0, see assay details)

50µl 10mM HEPES pH 7.4

25µl (50mg) SPA beads (Amersham)

100µl s-$\alpha_2\delta$-1b-6His of SEQ ID No 9 (2µl protein diluted to 100µl) obtained from example 5

25µl radioligand ([^{3}H]gabapentin)

Immediately after adding radioligand, the optiplates were loaded in the Packard Top Count scintillation counter to follow the binding time course. Imidazole was first used in the assay to optimize the specific interaction of the protein's 6His tag with the SPA bead. Imidazole itself (up to 100mM) in the filtration assay has no effect on [^{3}H]gabapentin binding (n=1).

As shown in figure 2, specific binding of [^{3}H]gabapentin to the s-$\alpha_2\delta$-1b-6His was enhanced by imidazole. Of the concentrations, tested the optimal was 50mM. Equilibration was reached after ~2hours.

Example 7

Ni Flashplate assay of [^{3}H]gabapentin binding to soluble porcine $\alpha_2\delta$-1b-6His (SEQ ID No 37)

Assays were carried out at 21°C in a final volume of 250µl in 96-well NEN Ni chelate flash plates. Assay components were added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25µl 10mM HEPES pH7.4

25µl imidazole at various concentrations (diluted from a 1M stock pH8.0, see assay details)

75µl 10mM HEPES pH 7.4

100µl s-$\alpha_2\delta$-1b-6His (2µl protein diluted to 100µl) obtained from example 5

25µl radioligand ([^{3}H]gabapentin)

Immediately after adding the radioligand, flash plates were loaded in the Packard Top Count scintillation counter to follow the binding time course. The '[^{3}H] flash plate' programme (cpm) was used to monitor activity. Imidazole was first used in the assay to optimize the specific interaction of the protein's 6His tag with the Ni flashplate. Imidazole itself (up to 100mM) in the filtration assay has no effect on [^{3}H]gabapentin binding (n=1).

As shown in figure 3, the specific binding of [^{3}H]gabapentin to the s-$\alpha_2\delta$-1b-6His was enhanced by imidazole. Initially, from the concentrations tested, the best concentration was found to be 10mM.

Specific binding was determined at different volumes of s-$\alpha_2\delta$-1b-6His, in the presence of 10mM imidazole, over a time period of 10h. Results are shown in figure 4 and equilibrium was reached at ~3h. Specific binding increased linearly with increasing amounts of protein, up to 8µl, after which the binding capacity of the Ni chelate in the assay well was probably exceeded (see figure 5). The published maximum binding capacity of NEN plates is 6pmol/well. The concentration of purified s-$\alpha_2\delta$-1b-6His is estimated at ~0.6pmol/µl, which yields 5pmol/well at 8µl.

Saturation experiments were performed with 12 duplicate data points, [^{3}H]gabapentin concentration ranged from ~1 to 350nM. Data was analyzed using KEL-RADLIG for Windows. The results are presented in Table 2 below.

Table 2

Saturation studies

Flash plate (2µl protein used, n=2)	**Filter binding** K_D(nM) (4µl protein used, n=3)
K_D, 9.32nM K_D, 10.5nM **Mean = 9.91nM**	K_D, 12.3nM K_D, 8.91nM K_D, 10.6nM **Mean = 10.60 ± 0.98nM**

Example 8

Ni Flashplate assay of [^{3}H]Leucine binding to soluble porcine $\alpha_2\delta$-1b-6His

The procedure described in example 2 was repeated, except that [^{3}H]gabapentin was replaced by 25 µl (10.1 nM) of [^{3}H]Leucine, as shown in figure 8, [^{3}H]Leucine binds with high affinity to soluble $\alpha_2\delta$-1b-6His. This demonstrates that it is possible to use commercially available forms of [^{3}H]Leucine in replacement of [^{3}H]gabapentin in the assay.

Example 9

Ni Flashplate assay studying competitive binding of [^{3}H]gabapentin, (S+)-3-isobutyl GABA and (R-)-3-isobutyl GABA to porcine $\alpha_2\delta$-1b-6His (SEQ ID No 9)

Assays were carried out at 21°C in a final volume of 250µl in 96-well NEN Ni chelate flash plates. Wells were set up for both 'total' and 'non-specific' binding. Specific binding was defined as that remaining after subtraction of the average of the 'non-specific binding' values from the average of the 'total' binding values. Assay components were added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25µl 10mM HEPES pH7.4 or 25 µl of the test compound at the appropriate concentration in HEPES

	25µl	200 mM imidazole (diluted from a 1M stock pH8.0, see assay details)
Total binding	75µl	10mM HEPES pH 7.4
Non-specific binding	50µl	10mM HEPES pH 7.4 and 25µl 100µM (S+)-3-isobutyl GABA
	100µl	s-$\alpha_2\delta$-1b-6His (2µl protein* diluted to 100µl)
	25µl	radioligand ([^{3}H]gabapentin or [^{3}H]Leucine)

* The source of s-$\alpha_2\delta$-1b-6His was that purified by FPLC Superdex-200 gel filtration (see example 5)

Immediately after adding radioligand, flash plates were loaded in the Packard Top Count scintillation counter to follow the binding time course. Incubation time before the assay was 3 hours. The '[^{3}H] flash plate' programme (cpm) was used to monitor activity. Specific binding was ~98% of the 'total' value. Imidazole was used in the assay to optimize the specific interaction of the protein's 6His tag with the Ni flashplate. Imidazole itself (up to 100mM) in the filtration assay has no effect on [^{3}H]gabapentin binding (n=1).

Competition studies were compared across the flash-plate and filter binding methodologies in order to validate the new assay technology with the established filter binding methodology.

GraphPad Prism software was used to process competition curve data and determine IC_{50} and hill slope values. Twelve point competition curves with half log dilution steps of test compounds were used in the experiments. Results are shown in Table 3 below where IC50 values are presented, and in figure 9 where hill slopes range from -0.9 to 1.3. The [^{3}H]Gabapentin concentration used in assay is in the range of 10-13nM

Table 3

Competition studies:

GraphPad Prism software was used to process competition curve data and determine IC_{50} and hill slope values. Ten point competition curves with half log dilution steps of test compounds were used in the experiments.

IC_{50} values were converted to Ki values (presented in table) according to the following equation:

$Ki = IC_{50} / (1+[L]/K_D)$

The K_D values used were those mean values presented in table 1.

The [^{3}H]Gabapentin concentration in the assay ranged from 10-13nM and was determined for each experiment for the purpose of calculating the Ki value as described above.

Hill slopes were all in the range of –0.9 to 1.3

Test compound	Flash plate (3µl protein used, n=2)	Filter binding K_D(nm) (4µl protein used, n=3)
Gabapentin	10.4 7.97	7.13 7.70 10.2
Mean (geometric)	***9.10nM***	***7.84nM***
(S+)-3-isobutyl GABA	10.9 7.58	6.52 6.21 8.29
Mean (geometric)	***9.09nM***	***6.95nM***
(R-)-3-isobtyl GABA	157 207	78.4 64.2 107
Mean (geometric)	***180nM***	***81.5nM***

Example 10

Filter binding assay of [^{3}H]gabapentin binding to the recombinant polypeptide of SEQ ID No 9

Assays were carried out at 21°C in a final volume of 250µl in 96-deep well plates. Assay components were (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25µl compound to test
200µl Polypeptide of SEQ ID No 9 (3µl protein diluted to 200µl)
25µl radioligand ([^{3}H]gabapentin (65Ci/mmole)

Plates were incubated at room temperature for 1h prior to filtering on to 96-well GF/B Unifilter plates pre-soaked in 0.3% polyethylenimine. Filters were washed with 3x1ml 50mM Tris-HCl (pH 7.4 at 4^{0}C), and dried over-night. Scintillant (Microscint O, 50µl) was added and the plates counted using a Packard Top Count scintillation counter. Specific binding was ~98% of the 'total' value. In [^{3}H]gabapentin saturation studies, the K_D (nM) obtained was about 10.62.

Example 11 :
Binding of [^{3}H]gabapentin to the recombinant polypeptide of SEQ ID No 37 using various assay formats.

This example further illustrates the screening method of this invention, using various assay formats.

a) Preparation of protein stocks

Protein was expressed as described in Example 4 except that the cells were infected at 1x10^6 cells/ml. Additionally the cells were cultured in 20 litre Applikon fermentation vessels (18L culture volume). The culture was maintained at 27°C and 60% dO2 (100% dO_2 equates to [O_2] when media - without cells - has been saturated with air at 27°C) with single marine impeller stirring at 125rpm. The protein was expressed in either Sf-900 II SFM (LTI Inc) or ESF-921 (Expression Systems Inc.) media.

b) Purification of s-$\alpha_2\delta$-1b-6His protein from cell culture supernatants

On the harvest day (day 4-7 post-infection with virus) the cell culture was centrifuged at 9,000xg for 20 minutes to remove the cellular debris, and the supernatant concentrated to

approximately 3 litres using a pellicon tangential-flow filtration system employing 30kDa cut-off regenerated-cellulose cassettes. The concentrated sample was re-centrifuged at 9,000xg for 20 minutes then diluted with 2 volumes of 10mM Tris (pH9.0). The diluted sample was then loaded at 10ml/min onto a Q-sepharose FF column (5cm i.d. x 50cm h.) which was washed with 20mM Tris-HCl (pH8.0) and eluted with 20mM Tris-HCl (pH8.0), 0.5M KCl, 10mM Imidazole.

The eluate was then loaded at 10ml/min onto a Ni-superflow (Qiagen) column (2.5cm i.d. x 6cm h.) pre-equilibrated in 20mM Tris (pH8.0), 0.1M KCl, 10mM Imidazole. The column was washed successively with buffer A (20mM Tris (pH8.0), 0.5M KCl, 20mM Imidazole), buffer B (20mM Tris-HCl (pH8.0), 1M KCl), and buffer A again at 10ml/min. Elution was performed with a gradient of buffer C (20mM Tris-HCl (pH8.0), 100mM KCl, 0.5M Imidazole) against 20mM Tris-HCl (pH8.0), 100mM KCl at 2ml/min (over 5 column volumes). Fractions from the gradient elution were assayed for [^{3}H]gabapentin binding activity and the active fractions pooled then dialysed at 4°C four times (each for 24 hours) against 10mM HEPES (pH7.3), 150mM NaCl at a ratio of 1:60 (sample:dialysate). The dialysed material was then aliquoted and frozen for use in the assays as described below.

c) Preparation of protein cocktails for filter, wheat germ lectin and Ni chelate assays (volumes in µl):

cocktail	x1		x23	
	s-$\alpha_2\delta$-1b-6His	HBS	**s-$\alpha_2\delta$-1b-6His**	**HBS**
0µl	0	75	**0**	**1,725**
1µl	1	74	**23**	**1,702**
2µl	2	73	**46**	**1,679**
4µl	4	71	**92**	**1,633**

$\alpha_2\delta$-1 protein was sourced from the aliquots generated above.

d) Filter and Wheat Germ Lectin flashplate assays

The reagents were added in the following order to each well of either a 96-well Wheat Germ Lectin flashplate or a 96-deep well plate. Conditions were prepared in triplicate for both 'total' and 'non-specific' binding (20µl H_2O added for total binding and 20µl of 100µM (S+)-3-isobutyl GABA to define non-specific binding) for each of the four volumes of protein tested.

Assay set-up per well:

100µM (S+)-3-isobutyl GABA / H_2O	20µl
*100nM [^{3}H]Gabapentin	20µl
235mM HEPES (pH7.3)	85µl
$\alpha_2\delta$-1 (0, 1, 2 or 4µl of the x23 cocktail)	75µl

* 20µl aliquots of the [^{3}H]gabapentin stock added to each well were counted on a liquid β-scintillation counter (Beckman LS 5000TD) to determine the actual concentration of [^{3}H]gabapentin reached in each well. For these experiments this value was calculated as 10.8nM.

The Wheat Germ lectin flashplate was then counted under continuous cycling conditions on a Packard Top Count Microplate scintillation counter. The plate was counted on the '[^{3}H]flashplate' programme with a count delay and count time of 1 minute. Data for the wheat germ lectin assay was plotted as 'specific' binding (i.e. 'total' minus 'non-specific binding'), see figure 10.

For the Filter assay, the binding reaction in the deep-well plate was left for 1 hour at 22°C then filtered with three 1ml washes of 4°C 50mM Tris (pH 7.4 at 4°C) onto a 96-well GF/B filter plate pre-soaked for 1 hour in 0.3% Polyethylenemine at 4°C. After leaving at 22°C to dry overnight, 45µl of Microscint-O (Packard) was added to each filter well and the plate sealed and counted in the Packard Top Count Microplate Scintillation counter on the '[^{3}H]Microscint' programme with a count delay and count time of 1 minute. The mean of the 'total' and 'non-specific' binding is presented in figure 11.

e) Nickel flashplate assay

2.35x Nickel flashplate buffer:

4.7ml	1M HEPES pH7.3
0.118ml	10% BSA (Sigma A7906, Fraction V (98%), Lot 57H1088) in H_2O
1.175ml	0.2M Imidazole pH7.3 (NaOH)
14.007ml	H_2O

Assay set-up per well:

100µM (S+)-3-isobutyl GABA / H_2O	20µl
*100nM [^{3}H]Gabapentin	20µl
2.35x Nickel Flashplate buffer	85µl
s-$\alpha_2\delta$-1b-6His (0, 1, 2 or 4µl of the x23 cocktail)	75µl

* 20µl aliquots of the [^{3}H]gabapentin stock added to each well were counted on a liquid β-scintillation counter (Beckman LS5000TD) to determine the actual concentration of [^{3}H]gabapentin reached in the each well. For these experiments this value was calculated as 10.8nM.

The Nickel flashplate was then counted under continuous cycling conditions on the Packard Top Count Microplate scintillation counter. The plate was counted on the '[^{3}H]flashplate' programme with a count delay and count time of 1 minute (Figure 12).

f) Discussion

This example demonstrates the extended stability of the assay over time (at least 100 hours), which is important if the assay format is to be used for mass-screening purposes. Indeed, such a stability enables the stacking of plates into counters (ideally with appropriate controls on each plate along with test compound wells in order to confirm signal stability across individual plates).

The example also shows that it is possible to use the Wheat Germ lectin flashplate assay, as a primary assay or as a secondary screen to further refine ligands identified or selected using the Ni flashplate assay or another assay format of this invention.

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CLAIMS:

1. A method for the screening of ligands which bind a cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$-1 subunit, said method comprising the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide with:
  - a ligand of interest; and
  - a labelled compound which binds the $\alpha_2\delta$-1 subunit; and
  - measuring the level of binding of the labelled compound to the $\alpha_2\delta$-1 subunit.

2. A method for the screening of biologically active products, in particular products that modulate a nervous system function in a subject, comprising the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide with:
  - a candidate product; and
  - a labelled compound which binds a $\alpha_2\delta$-1 subunit; and
  - -measuring the level of binding of the labelled compound to the secreted soluble $\alpha_2\delta$-1 subunit.

3. A method according to claims 1 or 2, wherein said method is an SPA assay.

4. A method according to claim 1 or 2, wherein said method is a flashplate assay.

5 A method according to claims 1 or 2 and 4 where the flashplate assay is a wheat germ lectin flashplate format.

6. A method according to claim 1or 2, wherein said method is a filter binding assay.

7. A method according to claim 1 or 2, wherein said secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide is selected from polypeptides having at least 80%, amino-acid identity with the polypeptide comprising from amino acid 1 to between

amino-acids 1008 and 1087, preferably between amino-acids 1018 and 1078, and most preferably between amino-acids 1043 and 1078 of SEQ ID N°33 or SEQ ID N°44.

8. A method according to claim 1 or 2, wherein said secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide is selected from the group consisting of SEQ ID N°34, 35, 36, 37, 41, 42 and 43 with the polypeptides of SEQ ID N°37 and SEQ ID N°43 being most preferred.

9 A method according to claims 1 or 2 , wherein the $\alpha 2\delta$-1 subunit polypeptide has at least 80% amino acid sequence identity of any of SEQ ID N°34, 35, 36, 37, 41, 42 and 43.

10. Use of C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST tagg for the purification and screening of $\alpha_2\delta$-1.

11. Use of C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST tagg for the purification and screening of $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 and 38.

12. Use of a sequence of histidine residues tagg for the purification and screening of $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 and 38.

13. Use of a sequence of 6 histidine residues tagg for the purification and screening of $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 and 38.

14. Use of C-terminal a 6 histidine residues tagg of $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 and 38 for purification and screening.

15. Use of nucleic acids encoding C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST taggs for the purification and screening of expressed $\alpha_2\delta$-1.

16. Use of nucleic acids encoding C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST tagg for the purification and screening of expressed $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 and 38.

17. Use of nucleic acids encoding a sequence of histidine residues tagg for the purification and screening of an expressed $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 and 38.

18. Use of a nucleic acid sequence encoding a sequence of 6 histidine residue tagg for the purification and screening of an expressed $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 and 38.

19. Use of the C-terminal part of a nucleic acid sequence encoding 6 histidine residue tagg of expressed $\alpha_2\delta$-1 of SEQ ID N°30, 31, 32, 33, 34, 35, 36, 37 and 38 for purification and screening.

20. Use of labelled compounds which have an affinity of less than 500nm for the gabapentin binding site of $\alpha 2\delta$-1 for the screening of ligands that bind to $\alpha 2\delta$-1.

21. Use according to claim 20, wherein the labelled compound is selected from labelled Gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine or L-Phenylalanine.

22. A method of screening of claims 1 or 2, wherein, the assay is conducted between 1 and 30°C.

23. A kit for the screening of ligands which bind a cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$-1 subunit, said kit comprising:

- a secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit; and
- a labelled compound which binds to the $\alpha_2\delta$-1 subunit.

24. A kit of claim 23, wherein the labelled compound is chosen from any one of the labelled compounds of claims 20 or 21.

25. A method for the screening of ligands which bind a cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$ subunit, said method comprising the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$ subunit polypeptide with:
  - a ligand of interest; and
  - a labelled compound which binds the $\alpha_2\delta$ subunit; and
  - measuring the level of binding of the labelled compound to the $\alpha_2\delta$ subunit.

26. A method for the screening of biologically active products, in particular products that modulate a nervous system function in a subject, comprising the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$ subunit polypeptide with:
  - a candidate product; and
  - a labelled compound which binds a $\alpha_2\delta$ subunit; and
  - -measuring the level of binding of the labelled compound to the secreted soluble $\alpha_2\delta$ subunit.

27. A method according to claims 25 or 26, wherein said method is an SPA assay.

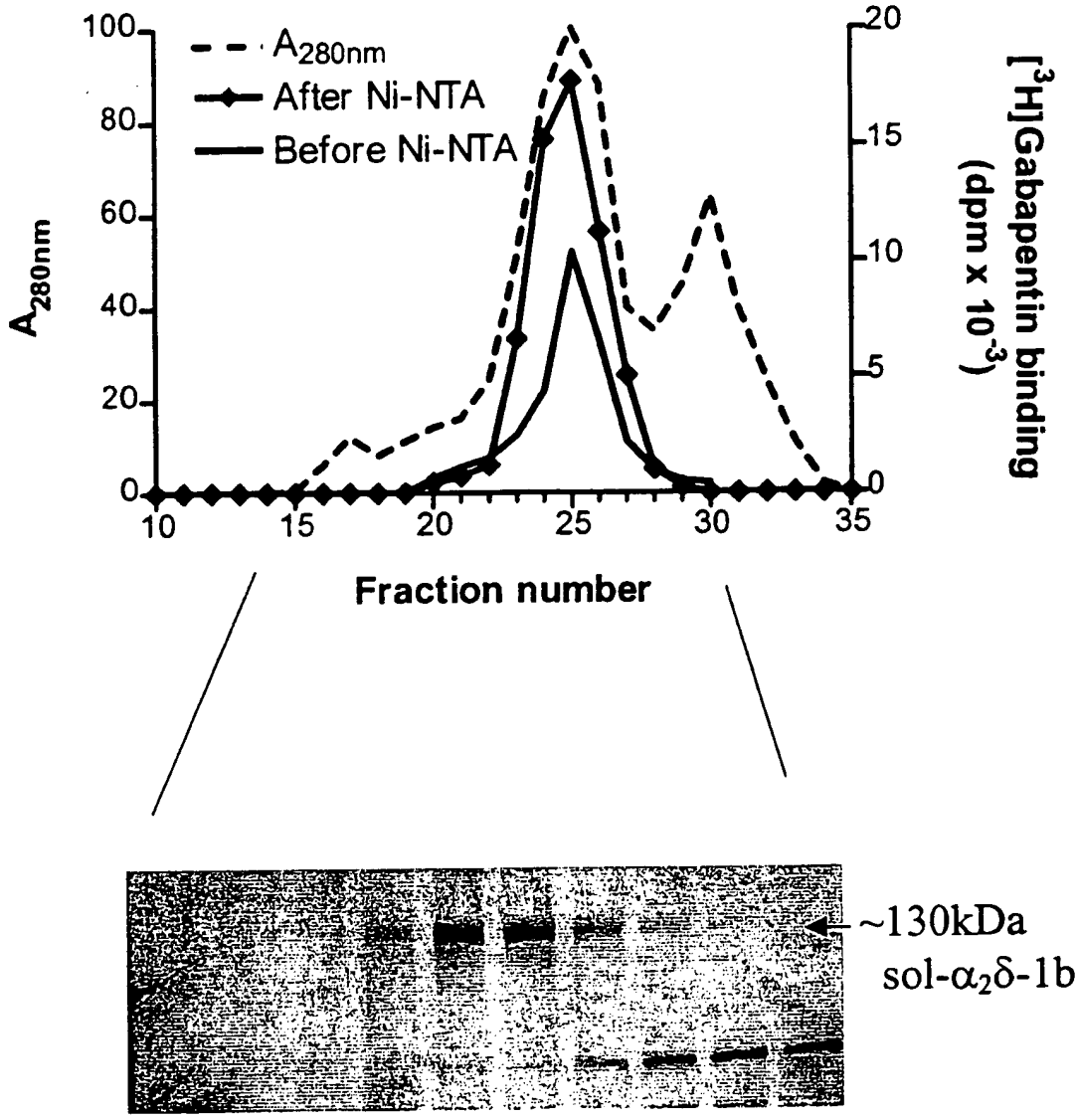
28. A method according to claim 25 or 26, wherein said method is a flashplate assay.

29. A kit for the screening of ligands which bind a cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$ subunit, said kit comprising:

- a secreted soluble recombinant calcium channel $\alpha_2\delta$ subunit; and
- a labelled compound which binds to the $\alpha_2\delta$ subunit.

30. A kit of claim 29, wherein the labelled compound is chosen from any one of the labelled compounds of claims 20 or 21.

FIGURE 1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60
40
20
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A_{280nm}
A_{280nm}
After Ni-NTA
Before Ni-NTA
20
15
10
5
0
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25
30
35
Fraction number
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sol-$\alpha_2\delta$-1b

FIGURE 2

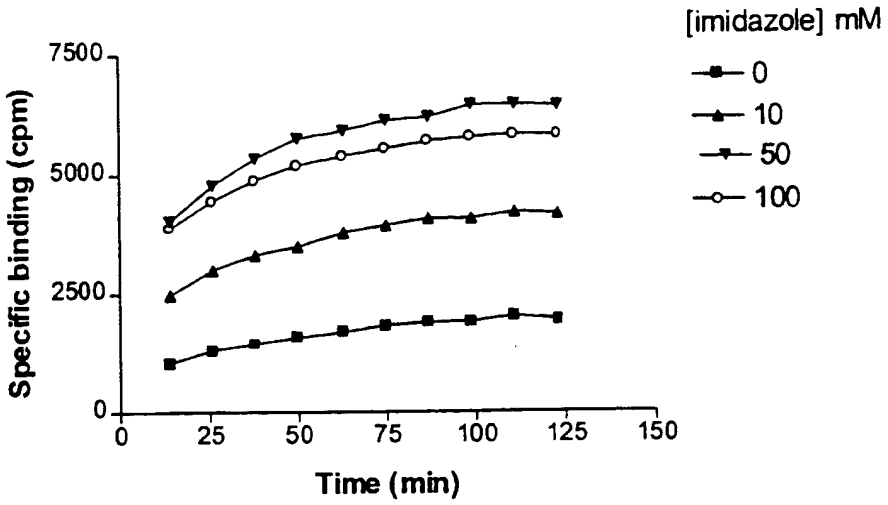
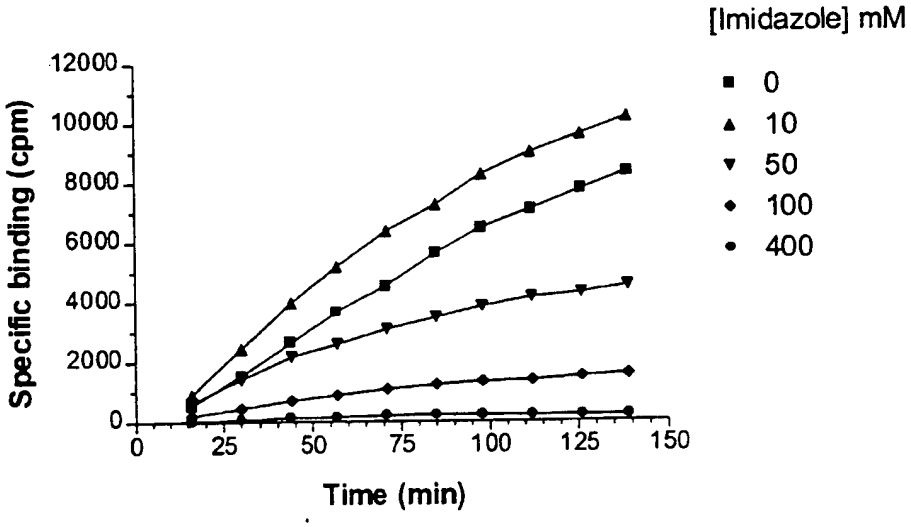


FIGURE 3



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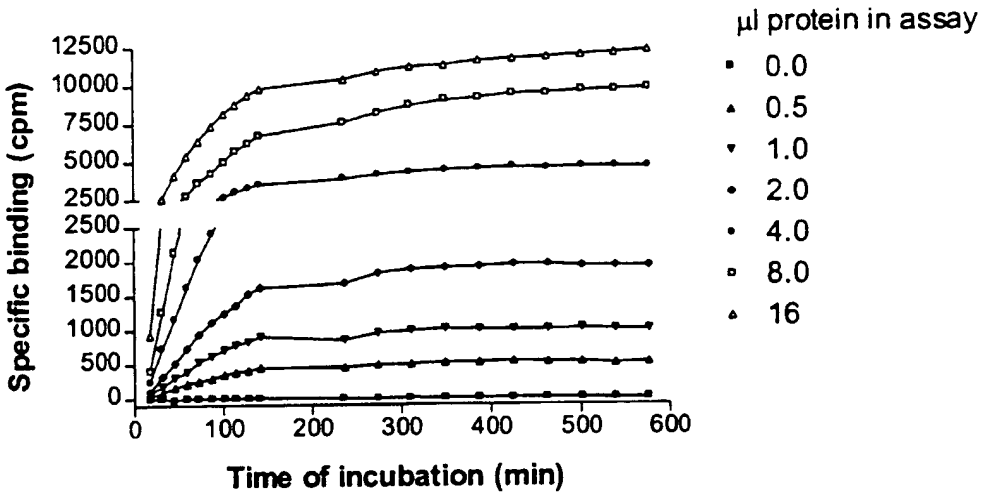
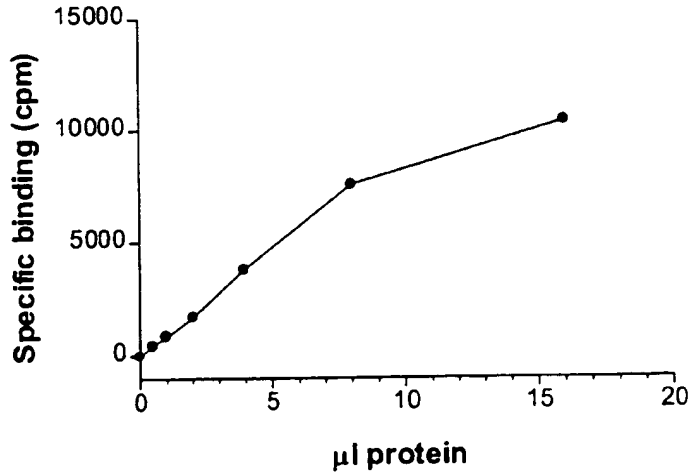


10mM imidazole in assay

FIGURE 5



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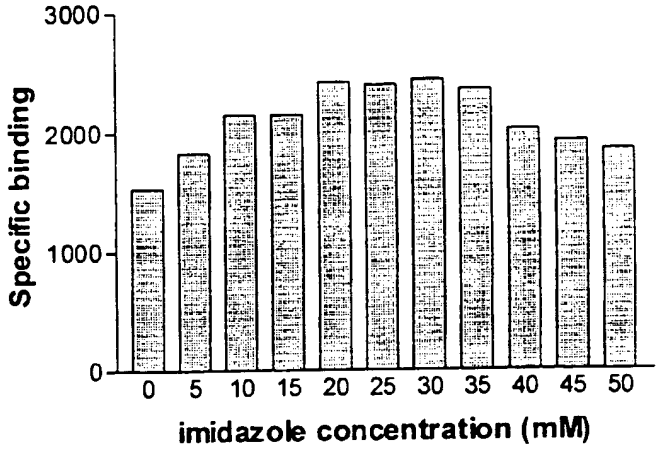


FIGURE 7

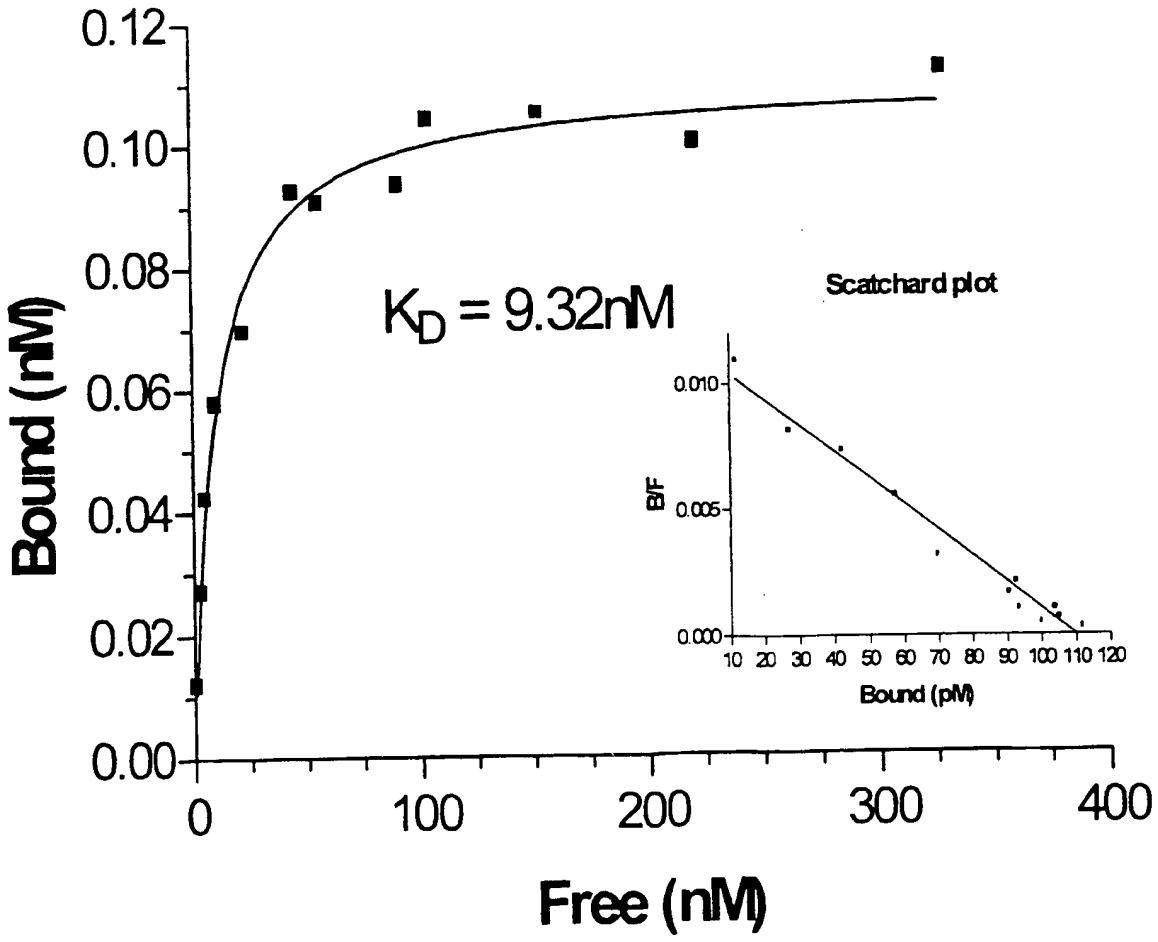
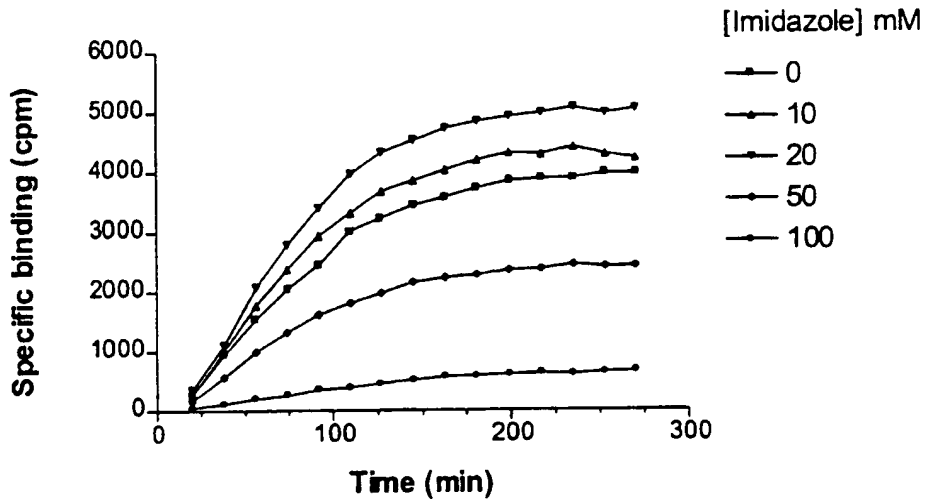


Figure 8



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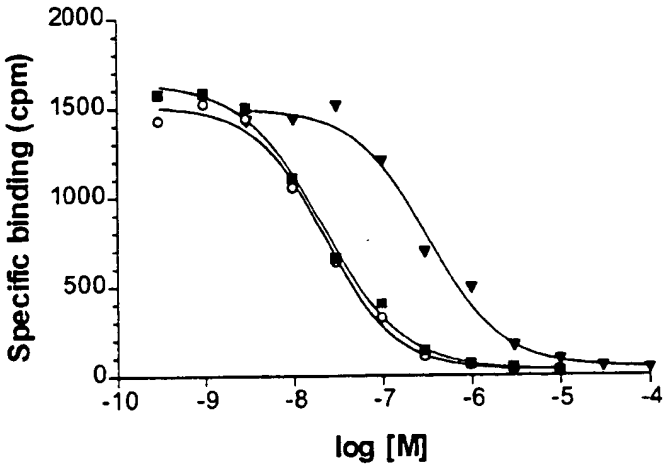
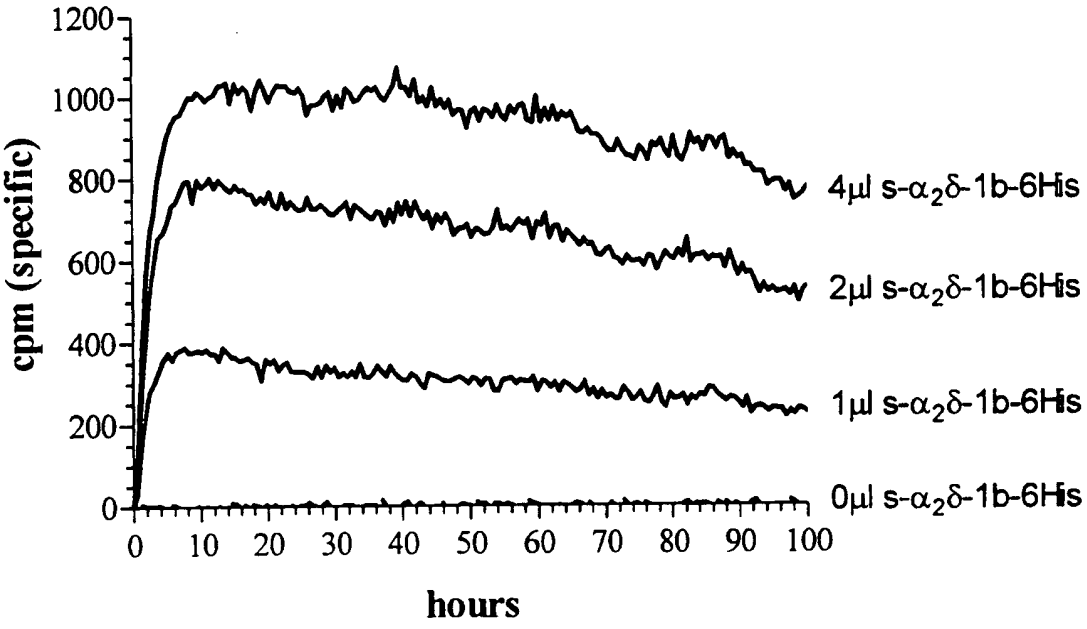


- ■ Gabapentin
- ○ (S+)-3-isobutyl GABA
- ▼ (R-)-3-isobutyl GABA

FIGURE 10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400
200
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10
20
30
40
50
60
70
80
90
100
hours
4µl s-α2δ-1b-6His
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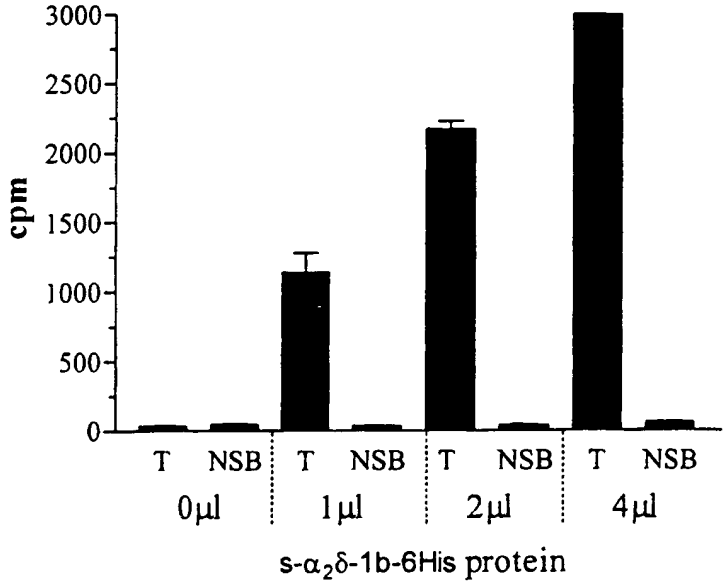
1µl s-α2δ-1b-6His
0µl s-α2δ-1b-6His

Figure 11



T -Total Binding
NSB -Non-Specific Binding

FIGURE 12

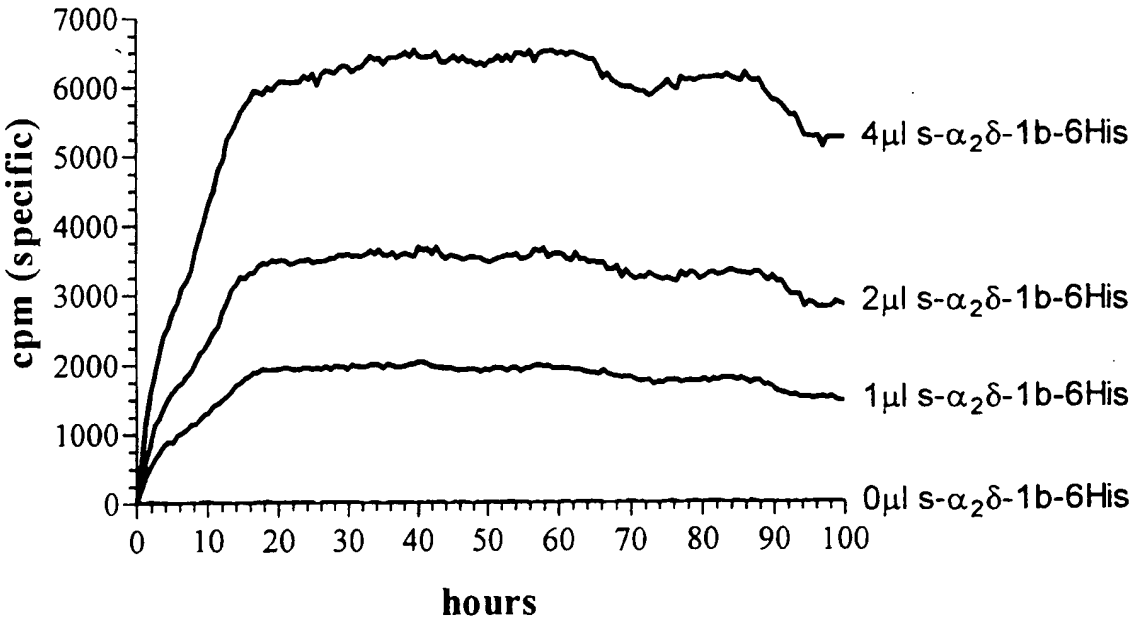


Figure 13

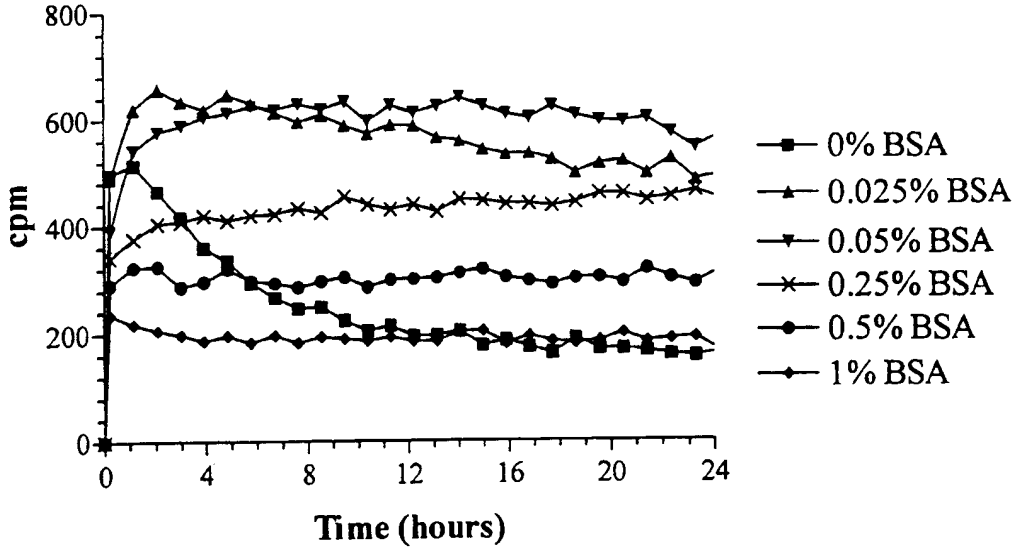


Figure 14

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Mouse-a2d1-splice-b	NNVLEDYTDC GGVS|GLNPSL WSIFGLQFIL LWLVSGSRHY LL*	
Rat-a2d1-splice-b	NNVLEDYTDC GGVS|GLNPSL WSIFGLQFIL LWLVSGSRHY LW*	

SEQUENCE LISTING

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ggccggctgc tgcagaagga gacgcactgc ccagcggacg gcccggagca gtgtgagcta 3240
gtgcagag 3248

<210> 3
<211> 3327
<212> DNA
<213> Homo sapiens

<400> 3
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ccgcgcccgc tgtggctgct gctgccgctt ctaccgctgc tcgccgcccc cggcgcctct 180
gcctacagct tcccccagca gcacacgatg cagcactggg cccggcgtct ggagcaggag 240
gtcgacggcg tgatgcggat ttttggaggc gtccagcagc tccgtgagat ttacaaggac 300
aaccggaacc tgttcgaggt acaggagaat gagcctcaga agttggtgga gaaggtggca 360
ggggacattg agagccttct ggacaggaag gtgcaggccc tgaagagact ggctgatgct 420
gcagagaact tccagaaagc acaccgctgg caggacaaca tcaaggagga agacatcgtg 480
tactatgacg ccaaggctga cgctgagctg gacgaccctg agagtgagga tgtggaaagg 540
gggtctaagg ccagcaccct aaggctggac ttcatcgagg acccaaactt caagaacaag 600
gtcaactatt catacgcggc tgtacagatc cctacggaca tctacaaagg ctccactgtc 660
atcctcaatg agctcaactg gacagaggcc ctggagaatg tgttcatgga aaaccgcaga 720
caagacccca cactgctgtg gcaggtcttc ggcagcgcca caggagtcac tcgctactac 780
ccggccaccc cgtggcgagc ccccaagaag atcgacctgt acgatgtccg aaggagaccc 840
tggtatatcc agggggcctc gtcacccaaa gacatggtca tcatcgtgga tgtgagtggc 900
agtgtgagcg gcctgaccct gaagctgatg aagacatctg tctgcgagat gctggacacg 960
ctgtctgatg atgactatgt gaatgtggcc tcgttcaacg agaaggcaca gcctgtgtca 1020
tgcttcacac acctggtgca ggccaatgtg cgcaacaaga aggtgttcaa ggaagctgtg 1080
cagggcatgg tggccaaggg caccacaggc tacaaggccg gctttgagta tgcctttgac 1140
cagctgcaga actccaacat cactcgggcc aactgcaaca agatgatcat gatgttcacg 1200
gatggtggtg aggaccgcgt gcaggacgtc tttgagaagt acaattggcc aaaccggacg 1260
gtgcgcgtgt ttactttctc cgtggggcag cataactatg acgtcacacc gctgcagtgg 1320
atggcctgtg ccaacaaagg ctactatttt gagatccctt ccatcggagc catccgcatc 1380
aacacacagg aatatctaga tgtgttgggc aggcccatgg tgctggcagg caaggaggcc 1440
aagcaggttc agtggaccaa cgtgtatgag gatgcactgg gactggggtt ggtggtaaca 1500
gggaccctcc ctgttttcaa cctgacacag gatggccctg gggaaaagaa gaaccagctg 1560
atcctgggcg tgatgggcat tgacgtggct ctgaatgaca tcaagaggct gaccccaac 1620
tacacgcttg gagccaacgg ctatgtgttt gccattgacc tgaacggcta cgtgttgctg 1680
caccccaatc tcaagcccca gaccaccaac ttccgggagc ctgtgactct ggacttcctg 1740
gatgcggagc tagaggatga gaacaaggaa gagatccgtc ggagcatgat tgatggcaac 1800
aagggccaca agcagatcag aacgttggtc aagtccctgg atgagaggta catagatgag 1860
gtgacacgga actacacctg ggtgcctata aggagcacta actacagcct ggggctggtg 1920
ctcccaccct acagcacctt ctacctccaa gccaatctca gtgaccagat cctgcaggtc 1980
aagtattttg agttcctgct ccccagcagc tttgagtctg aaggacacgt tttcattgct 2040
cccagagagt actgcaagga cctgaatgcc tcagacaaca acaccgagtt cctgaaaaac 2100
tttattgagc tcatggagaa agtgactcca gactccaagc agtgcaacaa cttccttctg 2160

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cacaacctga tcttggacac gggcatcacg cagcagctgg tagagcgtgt gtggagggac 2220
caggatctca acacgtacag cctactggcc gtgttcgctg ccacagacgg tggcatcacc 2280
cgagtcttcc ccaacaaggc agctgaggac tggacagaga accctgagcc cttcaatgcc 2340
agcttctacc gccgcagcct ggataaccac ggttatgtct tcaagccccc acaccaggat 2400
gccctgttaa ggccgctgga gctggagaat gacactgtgg gcatcctcgt cagcacagct 2460
gtggagctca gcctaggcag gcgcacactg aggccagcag tggtgggcgt caagctggac 2520
ctagaggctt gggctgagaa gttcaaggtg ctagccagca accgtaccca ccaagaccag 2580
cctcagaagt gcggccccaa cagccactgt gagatggact gcgaggttaa caatgaggac 2640
ttactctgtg tcctcattga tgatggagga ttcctggtgc tgtcaaacca gaaccatcag 2700
tgggaccagg tgggcaggtt cttcagtgag gtggatgcca acctgatgct ggcactctac 2760
aataactcct tctacacccg caaggagtcc tatgactatc aggcagcctg tgcccctcag 2820
ccccctggca acctgggtgc tgcaccccgg ggtgtctttg tgcccaccgt tgcagatttc 2880
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acgcgcgaga gcagctgcgt catgaaacag acccagtact acttcggctc ggtaaacgcc 3060
tcctacaacg ccatcatcga ctgcggaaac tgctccaggc tgttccacgc gcagagactg 3120
accaacacca atcttctctt tgtggtggcc gagaagccgc tgtgcagcca gtgcgaggct 3180
ggccggctgc tgcagaagga gacgcactgc ccagcggacg gcccggagca gtgtgagcta 3240
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gatacctcag actgtggccg cggggcc                                     3327
```

<210> 4
<211> 1062
<212> PRT
<213> Homo sapiens

<400> 4

```
Met Ala Val Pro Ala Arg Thr Cys Gly Ala Ser Arg Pro Gly Pro Ala
  1               5                  10                  15

Arg Thr Ala Arg Pro Trp Pro Gly Cys Gly Pro His Pro Gly Pro Gly
             20                  25                  30

Thr Arg Arg Pro Thr Ser Gly Pro Pro Arg Pro Leu Trp Leu Leu Leu
         35                  40                  45

Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
     50                  55                  60

Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
 65                  70                  75                  80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
                 85                  90                  95

Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
            100                 105                 110

Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
        115                 120                 125

Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
    130                 135                 140

Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
145                 150                 155                 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
                165                 170                 175
```

```
Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
            180                 185                 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
        195                 200                 205

Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
    210                 215                 220

Leu Asn Trp Thr Glu Ala Leu Glu Asn Val Phe Met Glu Asn Arg Arg
225                 230                 235                 240

Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
                245                 250                 255

Thr Arg Tyr Tyr Pro Ala Thr Pro Trp Arg Ala Pro Lys Lys Ile Asp
            260                 265                 270

Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
        275                 280                 285

Pro Lys Asp Met Val Ile Ile Val Asp Val Ser Gly Ser Val Ser Gly
    290                 295                 300

Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
305                 310                 315                 320

Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
                325                 330                 335

Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn
            340                 345                 350

Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
        355                 360                 365

Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn
    370                 375                 380

Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
385                 390                 395                 400

Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
                405                 410                 415

Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
            420                 425                 430

Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
        435                 440                 445

Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
    450                 455                 460

Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
465                 470                 475                 480

Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
                485                 490                 495

Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
```

500 505 510

Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
515 520 525

Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
530 535 540

Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
545 550 555 560

His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
565 570 575

Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
580 585 590

Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
595 600 605

Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
610 615 620

Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
625 630 635 640

Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
645 650 655

Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
660 665 670

Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
675 680 685

Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu
690 695 700

Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
705 710 715 720

His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg
725 730 735

Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe
740 745 750

Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala
755 760 765

Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
770 775 780

Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp
785 790 795 800

Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu
805 810 815

Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
820 825 830

```
Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
        835                 840                 845

Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys
    850                 855                 860

Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp
865                 870                 875                 880

Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn
                885                 890                 895

Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp
            900                 905                 910

Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys
        915                 920                 925

Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn
    930                 935                 940

Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe
945                 950                 955                 960

Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln
                965                 970                 975

Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro
            980                 985                 990

Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
        995                1000                1005

Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
   1010                1015                1020

Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
1025                1030                1035                1040

Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
                1045                1050                1055

Gln Cys Glu Ala Gly Arg
            1060
```

<210> 5
<211> 1082
<212> PRT
<213> Homo sapiens

<400> 5

```
Met Ala Val Pro Ala Arg Thr Cys Gly Ala Ser Arg Pro Gly Pro Ala
  1               5                  10                  15

Arg Thr Ala Arg Pro Trp Pro Gly Cys Gly Pro His Pro Gly Pro Gly
             20                  25                  30

Thr Arg Arg Pro Thr Ser Gly Pro Pro Arg Pro Leu Trp Leu Leu Leu
         35                  40                  45
```

```
Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
     50                  55                  60

Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
 65                  70                  75                  80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
                 85                  90                  95

Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
            100                 105                 110

Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
        115                 120                 125

Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
    130                 135                 140

Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
145                 150                 155                 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
                165                 170                 175

Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
            180                 185                 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
        195                 200                 205

Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
    210                 215                 220

Leu Asn Trp Thr Glu Ala Leu Glu Asn Val Phe Met Glu Asn Arg Arg
225                 230                 235                 240

Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
                245                 250                 255

Thr Arg Tyr Tyr Pro Ala Thr Pro Trp Arg Ala Pro Lys Lys Ile Asp
            260                 265                 270

Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
        275                 280                 285

Pro Lys Asp Met Val Ile Ile Val Asp Val Ser Gly Ser Val Ser Gly
    290                 295                 300

Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
305                 310                 315                 320

Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
                325                 330                 335

Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn
            340                 345                 350

Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
        355                 360                 365
```

Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn
370 375 380

Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
385 390 395 400

Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
405 410 415

Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
420 425 430

Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
435 440 445

Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
450 455 460

Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
465 470 475 480

Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
485 490 495

Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
500 505 510

Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
515 520 525

Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
530 535 540

Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
545 550 555 560

His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
565 570 575

Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
580 585 590

Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
595 600 605

Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
610 615 620

Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
625 630 635 640

Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
645 650 655

Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
660 665 670

Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
675 680 685

Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu

690 695 700

Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
705 710 715 720

His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg
725 730 735

Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe
740 745 750

Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala
755 760 765

Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
770 775 780

Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp
785 790 795 800

Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu
805 810 815

Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
820 825 830

Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
835 840 845

Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys
850 855 860

Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp
865 870 875 880

Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn
885 890 895

Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp
900 905 910

Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys
915 920 925

Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn
930 935 940

Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe
945 950 955 960

Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln
965 970 975

Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro
980 985 990

Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
995 1000 1005

Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
1010 1015 1020

```
Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
1025               1030                1035                1040

Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
                1045                1050                1055

Gln Cys Glu Ala Gly Arg Leu Leu Gln Lys Glu Thr His Cys Pro Ala
            1060                1065                1070

Asp Gly Pro Glu Gln Cys Glu Leu Val Gln
        1075                1080
```

<210> 6
<211> 1109
<212> PRT
<213> Homo sapiens

<400> 6

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Met Ala Val Pro Ala Arg Thr Cys Gly Ala Ser Arg Pro Gly Pro Ala
  1               5                  10                  15

Arg Thr Ala Arg Pro Trp Pro Gly Cys Gly Pro His Pro Gly Pro Gly
             20                  25                  30

Thr Arg Arg Pro Thr Ser Gly Pro Pro Arg Pro Leu Trp Leu Leu Leu
         35                  40                  45

Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
     50                  55                  60

Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
 65                  70                  75                  80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
                 85                  90                  95

Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
            100                 105                 110

Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
        115                 120                 125

Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
    130                 135                 140

Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
145                 150                 155                 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
                165                 170                 175

Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
            180                 185                 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
        195                 200                 205

Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
    210                 215                 220
```

```
Leu Asn Trp Thr Glu Ala Leu Glu Asn Val Phe Met Glu Asn Arg Arg
225                 230                 235                 240

Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
                245                 250                 255

Thr Arg Tyr Tyr Pro Ala Thr Pro Trp Arg Ala Pro Lys Lys Ile Asp
            260                 265                 270

Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
        275                 280                 285

Pro Lys Asp Met Val Ile Ile Val Asp Val Ser Gly Ser Val Ser Gly
    290                 295                 300

Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
305                 310                 315                 320

Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
                325                 330                 335

Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn
            340                 345                 350

Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
        355                 360                 365

Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn
    370                 375                 380

Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
385                 390                 395                 400

Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
                405                 410                 415

Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
            420                 425                 430

Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
        435                 440                 445

Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
    450                 455                 460

Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
465                 470                 475                 480

Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
                485                 490                 495

Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
            500                 505                 510

Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
        515                 520                 525

Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
    530                 535                 540
```

Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
545 550 555 560

His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
565 570 575

Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
580 585 590

Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
595 600 605

Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
610 615 620

Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
625 630 635 640

Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
645 650 655

Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
660 665 670

Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
675 680 685

Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu
690 695 700

Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
705 710 715 720

His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg
725 730 735

Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe
740 745 750

Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala
755 760 765

Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
770 775 780

Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp
785 790 795 800

Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu
805 810 815

Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
820 825 830

Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
835 840 845

Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys
850 855 860

Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp

865 870 875 880

Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn
885 890 895

Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp
900 905 910

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Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
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Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
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Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
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Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
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Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
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Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
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Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
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Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
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Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
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Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
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Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
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Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
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Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
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Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
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Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
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Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
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1 5 10 15

Leu Leu Ala Ala Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg
20 25 30

Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
35 40 45

Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
50 55 60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
65 70 75 80

Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
85 90 95

Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
100 105 110

Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
115 120 125

Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
130 135 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
145 150 155 160

Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
165 170 175

Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
180 185 190

Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
195 200 205

Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
210 215 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
225 230 235 240

Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
245 250 255

Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
260 265 270

Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
275 280 285

```
Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
    290                 295                 300

Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
305                 310                 315                 320

Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
                325                 330                 335

Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
            340                 345                 350

Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
        355                 360                 365

Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
    370                 375                 380

Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
385                 390                 395                 400

Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
                405                 410                 415

Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
            420                 425                 430

Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
        435                 440                 445

Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp
    450                 455                 460

Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys
465                 470                 475                 480

Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr
                485                 490                 495

Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu
            500                 505                 510

Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu
        515                 520                 525

Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg
    530                 535                 540

Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
545                 550                 555                 560

Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
                565                 570                 575

Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
            580                 585                 590

Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
        595                 600                 605

Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
```

610 615 620

Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
625 630 635 640

Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
645 650 655

Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys
660 665 670

Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
675 680 685

Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
690 695 700

Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
705 710 715 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
725 730 735

Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
740 745 750

Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
755 760 765

Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
770 775 780

Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
785 790 795 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
805 810 815

Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
820 825 830

Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val
835 840 845

Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
850 855 860

Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met
865 870 875 880

Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp
885 890 895

Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His
900 905 910

Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile
915 920 925

Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp
930 935 940

```
Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu
945                 950                 955                 960

Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile
                965                 970                 975

Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe
            980                 985                 990

Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp
        995                1000                1005

Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile Thr Met Ala Pro Ile
   1010                1015                1020

Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys Glu Arg Leu Lys
1025                1030                1035
```

<210> 12
<211> 1065
<212> PRT
<213> Homo sapiens

<400> 12

```
Met Ala Gly Pro Gly Ser Pro Arg Arg Ala Ser Arg Gly Ala Ser Ala
  1               5                  10                  15

Leu Leu Ala Ala Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg
             20                  25                  30

Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
         35                  40                  45

Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
     50                  55                  60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
 65                  70                  75                  80

Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
                 85                  90                  95

Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
            100                 105                 110

Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
        115                 120                 125

Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
    130                 135                 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
145                 150                 155                 160

Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
                165                 170                 175

Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
            180                 185                 190
```

```
Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
        195                 200                 205

Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
    210                 215                 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
225                 230                 235                 240

Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
                245                 250                 255

Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
            260                 265                 270

Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
        275                 280                 285

Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
    290                 295                 300

Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
305                 310                 315                 320

Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
                325                 330                 335

Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
            340                 345                 350

Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
        355                 360                 365

Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
    370                 375                 380

Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
385                 390                 395                 400

Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
                405                 410                 415

Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
            420                 425                 430

Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
        435                 440                 445

Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp
    450                 455                 460

Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys
465                 470                 475                 480

Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr
                485                 490                 495

Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu
            500                 505                 510
```

Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu
515 520 525

Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg
530 535 540

Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
545 550 555 560

Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
565 570 575

Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
580 585 590

Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
595 600 605

Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
610 615 620

Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
625 630 635 640

Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
645 650 655

Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys
660 665 670

Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
675 680 685

Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
690 695 700

Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
705 710 715 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
725 730 735

Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
740 745 750

Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
755 760 765

Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
770 775 780

Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
785 790 795 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
805 810 815

Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
820 825 830

Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val

```
        835                 840                 845

Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
    850                 855                 860

Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met
865                 870                 875                 880

Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp
                885                 890                 895

Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His
            900                 905                 910

Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile
        915                 920                 925

Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp
    930                 935                 940

Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu
945                 950                 955                 960

Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile
                965                 970                 975

Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe
            980                 985                 990

Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp
        995                1000                1005

Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile Thr Met Ala Pro Ile
   1010                1015                1020

Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys Glu Arg Leu Lys Ala Gln
1025                1030                1035                1040

Lys Ile Arg Arg Arg Pro Glu Ser Cys His Gly Phe His Pro Glu Glu
                1045                1050                1055

Asn Ala Arg Glu Cys Gly Gly Ala Pro
            1060                1065
```

<210> 13
<211> 912
<212> DNA
<213> Homo sapiens

<400> 13
agtggcctcc tgagaagcag cttgttcgtg ggctccgaga aggtctccga caggaagttc 60
ctgacacctg aggacgaggc cagcgtgttc accctggacc gcttcccgct gtggtaccgc 120
caggcctcag agcatcctgc tggcagcttc gtcttcaacc tccgctgggc agaaggacca 180
gaaagtgcgg gtgaacccat ggtggtgacg gcaagcacag ctgtggcggt gaccgtggac 240
aagaggacag ccattgctgc agccgcgggc gtccaaatga agctggaatt cctccagcgc 300
aaattctggg cggcaacgcg gcagtgcagc actgtggatg ggccgtgcac acagagctgc 360
gaggacagtg atctggactg cttcgtcatc gacaacaacg ggttcattct gatctccaag 420
aggtcccgag agacgggaag atttctgggg gaggtggatg gtgctgtcct gacccagctg 480
ctcagcatgg gggtgttcag ccaagtgact atgtatgact atcaggccat gtgcaaaccc 540
tcgagtcacc accacagtgc agcccagccc ctggtcagcc caatttctgc cttcttgacg 600

gcgaccaggt ggctgctgca ggagctggtg ctgttcctgc tggagtggag tgtctggggc 660
tcctggtacg acagaggggc cgaggccaaa agtgtcttcc atcactccca caaacacaag 720
aagcaggacc cgctgcagcc ctgcgacacg gagtaccccg tgttcgtgta ccagccggcc 780
atccgggagg ccaacgggat cgtggagtgc gggccctgcc agaaggtatt tgtggtgcag 840
cagattccca acagtaacct cctcctcctg gtgacagacc ccacctgtga ctgcagcatc 900
ttcccaccag tg 912

<210> 14
<211> 969
<212> DNA
<213> Homo sapiens

<400> 14
agtggcctcc tgagaagcag cttgttcgtg ggctccgaga aggtctccga caggaagttc 60
ctgacacctg aggacgaggc cagcgtgttc accctggacc gcttcccgct gtggtaccgc 120
caggcctcag agcatcctgc tggcagcttc gtcttcaacc tccgctgggc agaaggacca 180
gaaagtgcgg gtgaacccat ggtggtgacg gcaagcacag ctgtggcggt gaccgtggac 240
aagaggacag ccattgctgc agccgcgggc gtccaaatga agctggaatt cctccagcgc 300
aaattctggg cggcaacgcg gcagtgcagc actgtggatg ggccgtgcac acagagctgc 360
gaggacagtg atctggactg cttcgtcatc gacaacaacg ggttcattct gatctccaag 420
aggtcccgag agacgggaag atttctgggg gaggtggatg gtgctgtcct gacccagctg 480
ctcagcatgg gggtgttcag ccaagtgact atgtatgact atcaggccat gtgcaaaccc 540
tcgagtcacc accacagtgc agcccagccc ctggtcagcc caatttctgc cttcttgacg 600
gcgaccaggt ggctgctgca ggagctggtg ctgttcctgc tggagtggag tgtctggggc 660
tcctggtacg acagaggggc cgaggccaaa agtgtcttcc atcactccca caaacacaag 720
aagcaggacc cgctgcagcc ctgcgacacg gagtaccccg tgttcgtgta ccagccggcc 780
atccgggagg ccaacgggat cgtggagtgc gggccctgcc agaaggtatt tgtggtgcag 840
cagattccca acagtaacct cctcctcctg gtgacagacc ccacctgtga ctgcagcatc 900
ttcccaccag tgctgcagga ggcgacagaa gtcaaatata atgcctctgt caaatgtgac 960
cggatgcgc 969

<210> 15
<211> 1050
<212> DNA
<213> Homo sapiens

<400> 15
agtggcctcc tgagaagcag cttgttcgtg ggctccgaga aggtctccga caggaagttc 60
ctgacacctg aggacgaggc cagcgtgttc accctggacc gcttcccgct gtggtaccgc 120
caggcctcag agcatcctgc tggcagcttc gtcttcaacc tccgctgggc agaaggacca 180
gaaagtgcgg gtgaacccat ggtggtgacg gcaagcacag ctgtggcggt gaccgtggac 240
aagaggacag ccattgctgc agccgcgggc gtccaaatga agctggaatt cctccagcgc 300
aaattctggg cggcaacgcg gcagtgcagc actgtggatg ggccgtgcac acagagctgc 360
gaggacagtg atctggactg cttcgtcatc gacaacaacg ggttcattct gatctccaag 420
aggtcccgag agacgggaag atttctgggg gaggtggatg gtgctgtcct gacccagctg 480
ctcagcatgg gggtgttcag ccaagtgact atgtatgact atcaggccat gtgcaaaccc 540
tcgagtcacc accacagtgc agcccagccc ctggtcagcc caatttctgc cttcttgacg 600
gcgaccaggt ggctgctgca ggagctggtg ctgttcctgc tggagtggag tgtctggggc 660
tcctggtacg acagaggggc cgaggccaaa agtgtcttcc atcactccca caaacacaag 720
aagcaggacc cgctgcagcc ctgcgacacg gagtaccccg tgttcgtgta ccagccggcc 780
atccgggagg ccaacgggat cgtggagtgc gggccctgcc agaaggtatt tgtggtgcag 840
cagattccca acagtaacct cctcctcctg gtgacagacc ccacctgtga ctgcagcatc 900
ttcccaccag tgctgcagga ggcgacagaa gtcaaatata atgcctctgt caaatgtgac 960
cggatgcgct cccagaagct ccgccggcga ccagactcct gccacgcctt ccatccagag 1020
gagaatgccc aggactgcgg cggcgcctcg 1050

<210> 16
<211> 304

<212> PRT
<213> Homo sapiens

<400> 16
Ser Gly Leu Leu Arg Ser Ser Leu Phe Val Gly Ser Glu Lys Val Ser
1 5 10 15

Asp Arg Lys Phe Leu Thr Pro Glu Asp Glu Ala Ser Val Phe Thr Leu
20 25 30

Asp Arg Phe Pro Leu Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly
35 40 45

Ser Phe Val Phe Asn Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly
50 55 60

Glu Pro Met Val Val Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp
65 70 75 80

Lys Arg Thr Ala Ile Ala Ala Ala Ala Gly Val Gln Met Lys Leu Glu
85 90 95

Phe Leu Gln Arg Lys Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val
100 105 110

Asp Gly Pro Cys Thr Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe
115 120 125

Val Ile Asp Asn Asn Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu
130 135 140

Thr Gly Arg Phe Leu Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu
145 150 155 160

Leu Ser Met Gly Val Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala
165 170 175

Met Cys Lys Pro Ser Ser His His His Ser Ala Ala Gln Pro Leu Val
180 185 190

Ser Pro Ile Ser Ala Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu
195 200 205

Leu Val Leu Phe Leu Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp
210 215 220

Arg Gly Ala Glu Ala Lys Ser Val Phe His His Ser His Lys His Lys
225 230 235 240

Lys Gln Asp Pro Leu Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val
245 250 255

Tyr Gln Pro Ala Ile Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro
260 265 270

Cys Gln Lys Val Phe Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu
275 280 285

Leu Leu Val Thr Asp Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val
290 295 300

<210> 17
<211> 323
<212> PRT
<213> Homo sapiens

<400> 17
Ser Gly Leu Leu Arg Ser Ser Leu Phe Val Gly Ser Glu Lys Val Ser
1 5 10 15

Asp Arg Lys Phe Leu Thr Pro Glu Asp Glu Ala Ser Val Phe Thr Leu
20 25 30

Asp Arg Phe Pro Leu Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly
35 40 45

Ser Phe Val Phe Asn Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly
50 55 60

Glu Pro Met Val Val Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp
65 70 75 80

Lys Arg Thr Ala Ile Ala Ala Ala Ala Gly Val Gln Met Lys Leu Glu
85 90 95

Phe Leu Gln Arg Lys Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val
100 105 110

Asp Gly Pro Cys Thr Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe
115 120 125

Val Ile Asp Asn Asn Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu
130 135 140

Thr Gly Arg Phe Leu Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu
145 150 155 160

Leu Ser Met Gly Val Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala
165 170 175

Met Cys Lys Pro Ser Ser His His His Ser Ala Ala Gln Pro Leu Val
180 185 190

Ser Pro Ile Ser Ala Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu
195 200 205

Leu Val Leu Phe Leu Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp
210 215 220

Arg Gly Ala Glu Ala Lys Ser Val Phe His His Ser His Lys His Lys
225 230 235 240

Lys Gln Asp Pro Leu Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val
245 250 255

Tyr Gln Pro Ala Ile Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro
260 265 270

```
Cys Gln Lys Val Phe Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu
        275                 280                 285

Leu Leu Val Thr Asp Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val
    290                 295                 300

Leu Gln Glu Ala Thr Glu Val Lys Tyr Asn Ala Ser Val Lys Cys Asp
305                 310                 315                 320

Arg Met Arg
```

<210> 18
<211> 350
<212> PRT
<213> Homo sapiens

<400> 18

```
Ser Gly Leu Leu Arg Ser Ser Leu Phe Val Gly Ser Glu Lys Val Ser
  1               5                  10                  15

Asp Arg Lys Phe Leu Thr Pro Glu Asp Glu Ala Ser Val Phe Thr Leu
             20                  25                  30

Asp Arg Phe Pro Leu Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly
         35                  40                  45

Ser Phe Val Phe Asn Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly
     50                  55                  60

Glu Pro Met Val Val Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp
 65                  70                  75                  80

Lys Arg Thr Ala Ile Ala Ala Ala Ala Gly Val Gln Met Lys Leu Glu
                 85                  90                  95

Phe Leu Gln Arg Lys Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val
            100                 105                 110

Asp Gly Pro Cys Thr Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe
        115                 120                 125

Val Ile Asp Asn Asn Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu
    130                 135                 140

Thr Gly Arg Phe Leu Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu
145                 150                 155                 160

Leu Ser Met Gly Val Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala
                165                 170                 175

Met Cys Lys Pro Ser Ser His His His Ser Ala Ala Gln Pro Leu Val
            180                 185                 190

Ser Pro Ile Ser Ala Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu
        195                 200                 205

Leu Val Leu Phe Leu Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp
    210                 215                 220
```

```
Arg Gly Ala Glu Ala Lys Ser Val Phe His His Ser His Lys His Lys
225                 230                 235                 240

Lys Gln Asp Pro Leu Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val
                245                 250                 255

Tyr Gln Pro Ala Ile Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro
            260                 265                 270

Cys Gln Lys Val Phe Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu
        275                 280                 285

Leu Leu Val Thr Asp Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val
    290                 295                 300

Leu Gln Glu Ala Thr Glu Val Lys Tyr Asn Ala Ser Val Lys Cys Asp
305                 310                 315                 320

Arg Met Arg Ser Gln Lys Leu Arg Arg Arg Pro Asp Ser Cys His Ala
                325                 330                 335

Phe His Pro Glu Glu Asn Ala Gln Asp Cys Gly Gly Ala Ser
            340                 345                 350
```

<210> 19
<211> 5482
<212> DNA
<213> Homo sapiens

<400> 19

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cgggcagcgc agcccgcaga ggcgctgcgg cccgtgcagc cccggaggcc cctcgcggag 60
aaggcggcgg cggaggagag gccgagttac cgcccgccgc ccgcgccccc ccaaccccgc 120
cgccgccgcc gccgccgcca ctgccccccc tccccgcggc gccgcatctt gaatggaaac 180
atggcggtgc cggctcggac ctgcggcgcc tctcggcccg gcccagcgcg gactgcgcgc 240
ccctggcccg gctgcggccc ccaccctggc cccggcaccc ggcgcccgac gtccgggccc 300
ccgcgcccgc tgtggctgct gctgccgctt ctaccgctgc tcgccgcccc cggcgcctct 360
gcctacagct tcccccagca gcacacgatg cagcactggg cccggcgtct ggagcaggag 420
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Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
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Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
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Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
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Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
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Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
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Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
180 185 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
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225 230 235 240

Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
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Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
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Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
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Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
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Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
420 425 430

Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
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Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
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Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
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Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
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Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
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Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
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Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
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Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
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Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys
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Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp
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Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn
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Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys
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Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
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Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
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Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
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Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
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Gln Cys Glu Ala Gly Arg Leu Leu Gln Lys Glu Thr His Cys Pro Ala
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Gly Pro His Ile Cys Phe Asp Tyr Asn Ala Thr Glu Asp Thr Ser Asp
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Cys Gly Arg Gly Ala Ser Phe Pro Pro Ser Leu Gly Val Leu Val Ser
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340 345 350

Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
355 360 365

Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
370 375 380

Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
385 390 395 400

Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
405 410 415

Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
420 425 430

Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
435 440 445

Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp
450 455 460

Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys
465 470 475 480

Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr
485 490 495

Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu
500 505 510

Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu
515 520 525

Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg
530 535 540

Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
545 550 555 560

Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
565 570 575

Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
580 585 590

Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
595 600 605

Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
610 615 620

Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
625 630 635 640

Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
645 650 655

Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys

660 665 670

Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
675 680 685

Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
690 695 700

Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
705 710 715 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
725 730 735

Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
740 745 750

Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
755 760 765

Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
770 775 780

Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
785 790 795 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
805 810 815

Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
820 825 830

Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val
835 840 845

Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
850 855 860

Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met
865 870 875 880

Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp
885 890 895

Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His
900 905 910

Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile
915 920 925

Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp
930 935 940

Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu
945 950 955 960

Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile
965 970 975

Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe
980 985 990

Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp
995 1000 1005

Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile Thr Met Ala Pro Ile
1010 1015 1020

Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys Glu Arg Leu Lys Ala Gln
1025 1030 1035 1040

Lys Ile Arg Arg Arg Pro Glu Ser Cys His Gly Phe His Pro Glu Glu
1045 1050 1055

Asn Ala Arg Glu Cys Gly Gly Ala Pro Ser Leu Gln Ala Gln Thr Val
1060 1065 1070

Leu Leu Leu Leu Pro Leu Leu Leu Met Leu Phe Ser Arg
1075 1080 1085

<210> 23
<211> 1115
<212> PRT
<213> Homo sapiens

<400> 23
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Arg Thr Ala Arg Pro Trp Pro Gly Cys Gly Pro His Pro Gly Pro Gly
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Thr Arg Arg Pro Thr Ser Gly Pro Pro Arg Pro Leu Trp Leu Leu Leu
35 40 45

Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
50 55 60

Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
65 70 75 80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
85 90 95

Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
100 105 110

Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
115 120 125

Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
130 135 140

Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
145 150 155 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
165 170 175

Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
180 185 190

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Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
        195                 200                 205

Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
    210                 215                 220

Leu Asn Trp Thr Glu Ala Leu Glu Asn Val Phe Met Glu Asn Arg Arg
225                 230                 235                 240

Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
                245                 250                 255

Thr Arg Tyr Tyr Pro Ala Thr Pro Trp Arg Ala Pro Lys Lys Ile Asp
            260                 265                 270

Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
        275                 280                 285

Pro Lys Asp Met Val Ile Ile Val Asp Val Ser Gly Ser Val Ser Gly
    290                 295                 300

Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
305                 310                 315                 320

Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
                325                 330                 335

Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn
            340                 345                 350

Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
        355                 360                 365

Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn
    370                 375                 380

Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
385                 390                 395                 400

Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
                405                 410                 415

Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
            420                 425                 430

Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
        435                 440                 445

Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
    450                 455                 460

Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
465                 470                 475                 480

Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
                485                 490                 495

Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
            500                 505                 510
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Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
515 520 525

Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
530 535 540

Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
545 550 555 560

His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
565 570 575

Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
580 585 590

Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
595 600 605

Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
610 615 620

Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
625 630 635 640

Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
645 650 655

Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
660 665 670

Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
675 680 685

Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu
690 695 700

Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
705 710 715 720

His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg
725 730 735

Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe
740 745 750

Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala
755 760 765

Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
770 775 780

Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp
785 790 795 800

Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu
805 810 815

Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
820 825 830

Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe

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        835                 840                 845

Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys
    850                 855                 860

Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp
865                 870                 875                 880

Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn
                885                 890                 895

Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp
            900                 905                 910

Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys
        915                 920                 925

Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn
    930                 935                 940

Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe
945                 950                 955                 960

Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln
                965                 970                 975

Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro
            980                 985                 990

Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
        995                1000                1005

Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
   1010                1015                1020

Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
1025                1030                1035                1040

Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
                1045                1050                1055

Gln Cys Glu Ala Gly Arg Leu Leu Gln Lys Glu Thr His Cys Pro Ala
            1060                1065                1070

Asp Gly Pro Glu Gln Cys Glu Leu Val Gln Arg Pro Arg Tyr Arg Arg
        1075                1080                1085

Gly Pro His Ile Cys Phe Asp Tyr Asn Ala Thr Glu Asp Thr Ser Asp
   1090                1095                1100

Cys Gly Arg Gly Ala His His His His His His
1105                1110                1115
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<211> 1077
<212> PRT
<213> Mus musculus

<400> 24
Met Ala Gly Pro Gly Ser Leu Cys Cys Ala Ser Arg Gly Ala Ser Ala

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Leu Leu Ala Thr Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg
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Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
        35                  40                  45

Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
    50                  55                  60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
65                  70                  75                  80

Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Ile Met Glu
                85                  90                  95

Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
            100                 105                 110

Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
        115                 120                 125

Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
    130                 135                 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
145                 150                 155                 160

Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
                165                 170                 175

Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
            180                 185                 190

Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
        195                 200                 205

Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
    210                 215                 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
225                 230                 235                 240

Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
                245                 250                 255

Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
            260                 265                 270

Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
        275                 280                 285

Asp Asp Phe Phe Asn Ile Ile Thr Tyr Asn Glu Glu Leu His Tyr Val
    290                 295                 300

Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
305                 310                 315                 320

Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
                325                 330                 335
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Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
340 345 350

Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
355 360 365

Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
370 375 380

Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
385 390 395 400

Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
405 410 415

Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
420 425 430

Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
435 440 445

Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Pro Gln Ala
450 455 460

Gln Lys Leu Ala Asp Asp Gln Gly Leu Val Leu Met Thr Thr Val Ala
465 470 475 480

Met Pro Val Phe Ser Lys Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu
485 490 495

Leu Gly Val Val Gly Thr Asp Val Pro Val Lys Glu Leu Leu Lys Thr
500 505 510

Ile Pro Lys Tyr Lys Leu Gly Ile His Gly Tyr Ala Phe Ala Ile Thr
515 520 525

Asn Asn Gly Tyr Ile Leu Thr His Pro Glu Leu Arg Pro Leu Tyr Glu
530 535 540

Glu Gly Lys Lys Arg Arg Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser
545 550 555 560

Glu Val Glu Trp Glu Asp Arg Asp Asp Val Leu Arg Asn Ala Met Val
565 570 575

Asn Arg Lys Thr Gly Lys Phe Ser Met Glu Val Lys Lys Thr Val Asp
580 585 590

Lys Gly Lys Arg Val Leu Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp
595 600 605

Ile Lys Gly Thr Pro Phe Ser Leu Gly Val Ala Leu Ser Arg Gly His
610 615 620

Gly Lys Tyr Phe Phe Arg Gly Asn Val Thr Ile Glu Glu Gly Leu His
625 630 635 640

Asp Leu Glu His Pro Asp Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys
645 650 655

Asn Thr Asp Leu His Pro Glu His Arg His Leu Ser Gln Leu Glu Ala
660 665 670

Ile Lys Leu Tyr Leu Lys Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys
675 680 685

Glu Leu Ile Gln Glu Val Leu Phe Asp Ala Val Val Ser Ala Pro Ile
690 695 700

Glu Ala Tyr Trp Thr Ser Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp
705 710 715 720

Lys Gly Val Glu Val Ala Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg
725 730 735

Ile Asn Leu Phe Val Gly Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu
740 745 750

Lys Ala Gly Asp Lys Glu Asn Ile Phe Asn Ala Asp His Phe Pro Leu
755 760 765

Trp Tyr Arg Arg Ala Ala Glu Gln Ile Ala Gly Ser Phe Val Tyr Ser
770 775 780

Ile Pro Phe Ser Thr Gly Thr Val Asn Lys Ser Asn Val Val Thr Ala
785 790 795 800

Ser Thr Ser Ile Gln Leu Leu Asp Glu Arg Lys Ser Pro Val Val Ala
805 810 815

Ala Val Gly Ile Gln Met Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp
820 825 830

Thr Ala Ser Arg Gln Cys Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser
835 840 845

Cys Asp Asp Glu Thr Val Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe
850 855 860

Ile Leu Val Ser Glu Asp Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu
865 870 875 880

Val Glu Gly Ala Val Met Asn Lys Leu Leu Thr Met Gly Ser Phe Lys
885 890 895

Arg Ile Thr Leu Tyr Asp Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu
900 905 910

Ser Ser Asp Ser Ala His Gly Leu Leu Asp Pro Tyr Lys Ala Phe Leu
915 920 925

Ser Ala Ala Lys Trp Ile Met Thr Glu Leu Val Leu Phe Leu Val Glu
930 935 940

Phe Asn Leu Cys Ser Trp Trp His Ser Asp Met Thr Ala Lys Ala Gln
945 950 955 960

Lys Leu Lys Gln Thr Leu Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe
965 970 975

Val Ser Glu Arg Thr Ile Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu

980 985 990

Asp Cys Ser Lys Ser Phe Val Ile Gln Gln Ile Pro Ser Ser Asn Leu
995 1000 1005

Phe Met Val Val Val Asp Ser Ser Cys Leu Cys Glu Ser Val Ala Pro
1010 1015 1020

Ile Thr Met Ala Pro Ile Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys
1025 1030 1035 1040

Glu Arg Leu Lys Ala Gln Lys Ile Arg Arg Arg Pro Glu Ser Cys His
1045 1050 1055

Gly Phe His Pro Glu Glu Asn Ala Arg Glu Cys Gly Gly Ala Ser His
1060 1065 1070

His His His His His
1075

<210> 25
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 25
tcgccaccat ggcggtgccg gctc 24

<210> 26
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 26
tcggaattcc tcagtgatgg tgatggtgat gggccccgcg gccacagtc 49

<210> 27
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 27
tcgccaccat ggccgggccg ggc 23

<210> 28
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 28
tctcagtgat ggtgatggtg atgcgatgca cccccacact ctc 43

<210> 29
<211> 3842
<212> DNA
<213> Sus scrofa

<400> 29
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aa 3842

<210> 30
<211> 3057
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<213> Sus scrofa

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Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
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Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe

195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
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Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
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Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
355 360 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

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Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
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Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
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Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
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Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
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Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

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Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
                565                 570                 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
            580                 585                 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
        595                 600                 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
    610                 615                 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625                 630                 635                 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
                645                 650                 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
            660                 665                 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
        675                 680                 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
    690                 695                 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705                 710                 715                 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
                725                 730                 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
            740                 745                 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
        755                 760                 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
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Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785                 790                 795                 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
                805                 810                 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
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Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
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Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
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Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
                885                 890                 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
            900                 905                 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
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Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
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Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
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Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Ala Leu Glu Asp Tyr
                1045                1050                1055

Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro Ser Leu Trp Ser Ile
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Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg

355 360 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
675 680 685

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Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
    690                 695                 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705                 710                 715                 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
                725                 730                 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
            740                 745                 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
        755                 760                 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
    770                 775                 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785                 790                 795                 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
                805                 810                 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
            820                 825                 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
        835                 840                 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
    850                 855                 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865                 870                 875                 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
                885                 890                 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
            900                 905                 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
        915                 920                 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                 1000                1005
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Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu
1010 1015

<210> 35
<211> 1036
<212> PRT
<213> Sus scrofa

<400> 35
Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
1 5 10 15

Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
20 25 30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
355 360 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser

595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
900 905 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

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Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
   1010                1015                1020

Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys
1025                1030                1035


<210> 36
<211> 1063
<212> PRT
<213> Sus scrofa

<400> 36
Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
  1               5                  10                  15

Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
            20                  25                  30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
        35                  40                  45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
    50                  55                  60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                85                  90                  95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175
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Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
    210                 215                 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
                325                 330                 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
            340                 345                 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
        355                 360                 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
    370                 375                 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385                 390                 395                 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
                405                 410                 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
            420                 425                 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
        435                 440                 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
    450                 455                 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465                 470                 475                 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
                485                 490                 495
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Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn

820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
900 905 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
1010 1015 1020

Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025 1030 1035 1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Ala Leu Glu Asp Tyr
1045 1050 1055

Thr Asp Cys Gly Gly Val Ser
1060

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Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
20 25 30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala

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        35                  40                  45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
     50                  55                  60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                 85                  90                  95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
    210                 215                 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
                325                 330                 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
            340                 345                 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
        355                 360                 365
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Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
900 905 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln

1010 1015 1020

Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025 1030 1035 1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Ala Leu Glu Asp Tyr
1045 1050 1055

Thr Asp Cys Gly Gly Val Ser His His His His His His
1060 1065

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<212> DNA
<213> Homo sapiens

<400> 38
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caagaagacc ttgtcacact ggcaaaaaca gcaagtggag tcaatcagct tgttgatatt 180
tatgagaaat atcaagattt gtatactgtg gaaccaaata atgcacgcca gctggtagaa 240
attgcagcca gggatattga gaaacttctg agcaacagat ctaaagccct ggtgagcctg 300
gcattggaag cggagaaagt tcaagcagct caccagtgga gagaagattt tgcaagcaat 360
gaagttgtct actacaatgc aaaggatgat ctcgatcctg agaaaaatga cagtgagcca 420
ggcagccaga ggataaaacc tgttttcatt gaagatgcta attttggacg acaaatatct 480
tatcagcacg cagcagtcca tattcctact gacatctatg agggctcaac aattgtgtta 540
aatgaactca actggacaag tgccttagat gaagttttca aaaagaatcg cgaggaagac 600
ccttcattat tgtggcaggt ttttggcagt gccactggcc tagctcgata ttatccagct 660
tcaccatggg ttgataatag tagaactcca aataagattg acctttatga tgtacgcaga 720
agaccatggt acatccaagg agctgcatct cctaaagaca tgcttattct ggtggatgtg 780
agtggaagtg ttagtggatt gacacttaaa ctgatccgaa catctgtctc cgaaatgtta 840
gaaaccctct cagatgatga tttcgtgaat gtagcttcat ttaacagcaa tgctcaggat 900
gtaagctgtt ttcagcacct tgtccaagca aatgtaagaa ataaaaaagt gttgaaagac 960
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Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
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Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
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Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
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Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
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Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
                645                 650                 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
            660                 665                 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
        675                 680                 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
    690                 695                 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705                 710                 715                 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
                725                 730                 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
            740                 745                 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
        755                 760                 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
    770                 775                 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785                 790                 795                 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
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805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
900 905 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
1010 1015 1020

Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys
1025 1030 1035

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<213> Homo sapiens

<400> 43
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Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr

50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
325 330 335

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340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
355 360 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
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Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
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Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
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Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
900 905 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
1010 1015 1020

Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys Gln Pro Arg Tyr

1025 1030 1035 1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr
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Thr Asp Cys Gly Gly Val Ser
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<212> PRT
<213> Homo sapiens

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35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile

245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
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Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
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Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
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Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
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Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
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Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
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Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
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Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
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Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
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Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

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Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
          900                 905                 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
        915                 920                 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
   1010                1015                1020

Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025                1030                1035                1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr
               1045                1050                1055

Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro Ser Leu Trp Tyr Ile
           1060                1065                1070

Ile Gly Ile Gln Phe Leu Leu Leu Trp Leu Val Ser Gly Ser Thr His
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<210> 45
<211> 3600
<212> DNA
<213> Homo sapiens

<400> 45

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<223> Description of Artificial Sequence:primer

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<210> 47
<211> 21

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 47
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<210> 48
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

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<210> 49
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

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<210> 50
<211> 3201
<212> DNA
<213> Homo sapiens

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Ile Tyr Pro Gly Ile Lys Trp Thr Pro Asp Glu Asn Gly Val Ile Thr
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Ala Tyr Trp Thr Ala Leu Ala Leu Asn Met Ser Glu Glu Ser Glu His
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Lys Lys Leu Lys Pro Lys Pro Asn Tyr Asn Ser Val Asp Leu Ser Glu
565 570 575

Val Glu Trp Glu Asp Gln Ala Glu Ser Leu Arg Thr Ala Met Ile Asn
580 585 590

Arg Glu Thr Gly Thr Leu Ser Met Asp Val Lys Val Pro Met Asp Lys
595 600 605

Gly Lys Arg Val Leu Phe Leu Thr Asn Asp Tyr Phe Phe Thr Asp Ile
610 615 620

Ser Asp Thr Pro Phe Ser Leu Gly Val Val Leu Ser Arg Gly His Gly
625 630 635 640

Glu Tyr Ile Leu Leu Gly Asn Thr Ser Val Glu Glu Gly Leu His Asp
645 650 655

Leu Leu His Pro Asp Leu Ala Leu Ala Gly Asp Trp Ile Tyr Cys Ile
660 665 670

Thr Asp Ile Asp Pro Asp His Arg Lys Leu Ser Gln Leu Glu Ala Met
675 680 685

Ile Arg Phe Leu Thr Arg Lys Asp Pro Asp Leu Glu Cys Asp Glu Glu
690 695 700

Leu Val Arg Glu Val Leu Phe Asp Ala Val Val Thr Ala Pro Met Glu
705 710 715 720

Ala Tyr Trp Thr Ala Leu Ala Leu Asn Met Ser Glu Glu Ser Glu His
725 730 735

Val Val Asp Met Ala Phe Leu Gly Thr Arg Ala Gly Leu Leu Arg Ser
740 745 750

Ser Leu Phe Val Gly Ser Glu Lys Val Ser Asp Arg Lys Phe Leu Thr
755 760 765

Pro Glu Asp Glu Ala Ser Val Phe Thr Leu Asp Arg Phe Pro Leu Trp
770 775 780

Tyr Arg Gln Ala Ser Glu His Pro Ala Gly Ser Phe Val Phe Asn Leu
785 790 795 800

Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly Glu Pro Met Val Val Thr
805 810 815

Ala Ser Thr Ala Val Ala Val Thr Val Asp Lys Arg Thr Ala Ile Ala
820 825 830

Ala Ala Ala Gly Val Gln Met Lys Leu Glu Phe Leu Gln Arg Lys Phe
835 840 845

Trp Ala Ala Thr Arg Gln Cys Ser Thr Val Asp Gly Pro Cys Thr Gln
850 855 860

Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe Val Ile Asp Asn Asn Gly
865 870 875 880

Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu Thr Gly Arg Phe Leu Gly
885 890 895

Glu Val Asp Gly Ala Val Leu Thr Gln Leu Leu Ser Met Gly Val Phe
900 905 910

Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala Met Cys Lys Pro Ser Ser
915 920 925

His His His Ser Ala Ala Gln Pro Leu Val Ser Pro Ile Ser Ala Phe
930 935 940

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Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu Leu Val Leu Phe Leu Leu
945                 950                 955                 960

Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp Arg Gly Ala Glu Ala Lys
                965                 970                 975

Ser Val Phe His His Ser His Lys His Lys Lys Gln Asp Pro Leu Gln
            980                 985                 990

Pro Cys Asp Thr Glu Tyr Pro Val Phe Val Tyr Gln Pro Ala Ile Arg
        995                1000                1005

Glu Ala Asn Gly Ile Val Glu Cys Gly Pro Cys Gln Lys Val Phe Val
   1010                1015                1020

Val Gln Gln Ile Pro Asn Ser Asn Leu Leu Leu Leu Val Thr Asp Pro
1025                1030                1035                1040

Thr Cys Asp Cys Ser Ile Phe Pro Pro Val Leu Gln Glu Ala Thr Glu
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Val Lys Tyr Asn Ala Ser Val Lys Cys Asp Arg Met Arg
            1060                1065
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<211> 1097
<212> PRT
<213> Homo sapiens

<400> 55

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Trp Ile Pro Leu Gln Pro Met Pro Val Ala Trp Ala Phe Val Gln Lys
             20                  25                  30

Thr Ser Ala Leu Leu Trp Leu Leu Leu Leu Gly Thr Ser Leu Ser Pro
         35                  40                  45

Ala Trp Gly Gln Ala Lys Ile Pro Leu Glu Thr Val Lys Leu Trp Ala
     50                  55                  60

Asp Thr Phe Gly Gly Asp Leu Tyr Asn Thr Val Thr Lys Tyr Ser Gly
 65                  70                  75                  80

Ser Leu Leu Leu Gln Lys Lys Tyr Lys Asp Val Glu Ser Ser Leu Lys
                 85                  90                  95

Ile Glu Glu Val Asp Gly Leu Glu Leu Val Arg Lys Phe Ser Glu Asp
            100                 105                 110

Met Glu Asn Met Leu Arg Arg Lys Val Glu Ala Val Gln Asn Leu Val
        115                 120                 125

Glu Ala Ala Glu Glu Ala Asp Leu Asn His Glu Phe Asn Glu Ser Leu
    130                 135                 140

Val Phe Asp Tyr Tyr Asn Ser Val Leu Ile Asn Glu Arg Asp Glu Lys
145                 150                 155                 160
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Gly Asn Phe Val Glu Leu Gly Ala Glu Phe Leu Leu Glu Ser Asn Ala
165 170 175

His Phe Ser Asn Leu Pro Val Asn Thr Ser Ile Ser Ser Val Gln Leu
180 185 190

Pro Thr Asn Val Tyr Asn Lys Asp Pro Asp Ile Leu Asn Gly Val Tyr
195 200 205

Met Ser Glu Ala Leu Asn Ala Val Phe Val Glu Asn Phe Gln Arg Asp
210 215 220

Pro Thr Leu Thr Trp Gln Tyr Phe Gly Ser Ala Thr Gly Phe Phe Arg
225 230 235 240

Ile Tyr Pro Gly Ile Lys Trp Thr Pro Asp Glu Asn Gly Val Ile Thr
245 250 255

Phe Asp Cys Arg Asn Arg Gly Trp Tyr Ile Gln Ala Ala Thr Ser Pro
260 265 270

Lys Asp Ile Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu
275 280 285

Arg Met Thr Ile Ala Lys His Thr Ile Thr Thr Ile Leu Asp Thr Leu
290 295 300

Gly Glu Asn Asp Phe Val Asn Ile Ile Ala Tyr Asn Asp Tyr Val His
305 310 315 320

Tyr Ile Glu Pro Cys Phe Lys Gly Ile Leu Val Gln Ala Asp Arg Asp
325 330 335

Asn Arg Glu His Phe Lys Leu Leu Val Glu Glu Leu Met Val Lys Gly
340 345 350

Val Gly Val Val Asp Gln Ala Leu Arg Glu Ala Phe Gln Ile Leu Lys
355 360 365

Gln Phe Gln Glu Ala Lys Gln Gly Ser Leu Cys Asn Gln Ala Ile Met
370 375 380

Leu Ile Ser Asp Gly Ala Val Glu Asp Tyr Glu Pro Val Phe Glu Lys
385 390 395 400

Tyr Asn Trp Pro Asp Cys Lys Val Arg Val Phe Thr Tyr Leu Ile Gly
405 410 415

Arg Glu Val Ser Phe Ala Asp Arg Met Lys Trp Ile Ala Cys Asn Asn
420 425 430

Lys Gly Tyr Tyr Thr Gln Ile Ser Thr Leu Ala Asp Thr Gln Glu Asn
435 440 445

Val Met Glu Tyr Leu His Val Leu Ser Arg Pro Met Val Ile Asn His
450 455 460

Asp His Asp Ile Ile Trp Thr Glu Ala Tyr Met Asp Ser Lys Leu Leu
465 470 475 480

Ser Ser Gln Ala Gln Ser Leu Thr Leu Leu Thr Thr Val Ala Met Pro

485 490 495

Val Phe Ser Lys Lys Asn Glu Thr Arg Ser His Gly Ile Leu Leu Gly
500 505 510

Val Val Gly Ser Asp Val Ala Leu Arg Glu Leu Met Lys Leu Ala Pro
515 520 525

Arg Tyr Lys Leu Gly Val His Gly Tyr Ala Phe Leu Asn Thr Asn Asn
530 535 540

Gly Tyr Ile Leu Ser His Pro Asp Leu Arg Pro Leu Tyr Arg Glu Gly
545 550 555 560

Lys Lys Leu Lys Pro Lys Pro Asn Tyr Asn Ser Val Asp Leu Ser Glu
565 570 575

Val Glu Trp Glu Asp Gln Ala Glu Ser Leu Arg Thr Ala Met Ile Asn
580 585 590

Arg Glu Thr Gly Thr Leu Ser Met Asp Val Lys Val Pro Met Asp Lys
595 600 605

Gly Lys Arg Val Leu Phe Leu Thr Asn Asp Tyr Phe Phe Thr Asp Ile
610 615 620

Ser Asp Thr Pro Phe Ser Leu Gly Val Val Leu Ser Arg Gly His Gly
625 630 635 640

Glu Tyr Ile Leu Leu Gly Asn Thr Ser Val Glu Glu Gly Leu His Asp
645 650 655

Leu Leu His Pro Asp Leu Ala Leu Ala Gly Asp Trp Ile Tyr Cys Ile
660 665 670

Thr Asp Ile Asp Pro Asp His Arg Lys Leu Ser Gln Leu Glu Ala Met
675 680 685

Ile Arg Phe Leu Thr Arg Lys Asp Pro Asp Leu Glu Cys Asp Glu Glu
690 695 700

Leu Val Arg Glu Val Leu Phe Asp Ala Val Val Thr Ala Pro Met Glu
705 710 715 720

Ala Tyr Trp Thr Ala Leu Ala Leu Asn Met Ser Glu Glu Ser Glu His
725 730 735

Val Val Asp Met Ala Phe Leu Gly Thr Arg Ala Ser Gly Leu Leu Arg
740 745 750

Ser Ser Leu Phe Val Gly Ser Glu Lys Val Ser Asp Arg Lys Phe Leu
755 760 765

Thr Pro Glu Asp Glu Ala Ser Val Phe Thr Leu Asp Arg Phe Pro Leu
770 775 780

Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly Ser Phe Val Phe Asn
785 790 795 800

Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly Glu Pro Met Val Val
805 810 815

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Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp Lys Arg Thr Ala Ile
            820                 825                 830

Ala Ala Ala Ala Gly Val Gln Met Lys Leu Glu Phe Leu Gln Arg Lys
        835                 840                 845

Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val Asp Gly Pro Cys Thr
    850                 855                 860

Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe Val Ile Asp Asn Asn
865                 870                 875                 880

Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu Thr Gly Arg Phe Leu
                885                 890                 895

Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu Leu Ser Met Gly Val
            900                 905                 910

Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala Met Cys Lys Pro Ser
        915                 920                 925

Ser His His His Ser Ala Ala Gln Pro Leu Val Ser Pro Ile Ser Ala
    930                 935                 940

Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu Leu Val Leu Phe Leu
945                 950                 955                 960

Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp Arg Gly Ala Glu Ala
                965                 970                 975

Lys Ser Val Phe His His Ser His Lys His Lys Lys Gln Asp Pro Leu
            980                 985                 990

Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val Tyr Gln Pro Ala Ile
        995                1000                1005

Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro Cys Gln Lys Val Phe
   1010                1015                1020

Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu Leu Leu Val Thr Asp
1025                1030                1035                1040

Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val Leu Gln Glu Ala Thr
                1045                1050                1055

Glu Val Lys Tyr Asn Ala Ser Val Lys Cys Asp Arg Met Arg Ser Gln
            1060                1065                1070

Lys Leu Arg Arg Arg Pro Asp Ser Cys His Ala Phe His Pro Glu Glu
        1075                1080                1085

Asn Ala Gln Asp Cys Gly Gly Ala Ser
   1090                1095
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